

Appendix 16.1.1 Protocol and protocol amendments

History of changes	
Version	Summary of changes
1.0	Original version

1 Protocols and protocol amendments

Table 1-1 List of protocols, protocol amendments and post text supplements

Document	Effective Date
Original Protocol (V1.0)	22-MAY-2018
Protocol amendment 1 (V2.0) (track changes version only)	16-JAN-2019
Protocol amendment 2 (V3.0) (track changes version only)	01-APR-2019
Protocol amendment 3 (V4.0) (track changes version)	09-APR-2019
Protocol amendment 3 (V4.0) (clean)	09-APR-2019
Protocol amendment 4* (V4.1 DE) (track changes version)	09-AUG-2019
Protocol amendment 4* (V4.1 DE) (clean)	09-AUG-2019
Protocol amendment 5* (V4.4 DE) (track changes version)	22-JUL-2020
Protocol amendment 5* (V4.4 DE) (clean)	22-JUL-2020
Imaging Endpoint Imaging Manual (V1.0)	17-MAY-2018
Imaging Endpoint Imaging Manual (V2.0)	28-JUN-2018
Imaging Endpoint Imaging Manual (V3.0)	07-FEB-2019
Imaging Endpoint Imaging Manual (V4.0)	11-JUL-2019

* Amendment V4.1 DE and V4.4 DE is a local amendment for Germany related to the sub-study non-randomized cohort.

2 Data monitoring committee (DMC)

Table 2-1 Data monitoring committee charters

Document	Effective Date
Data monitoring committee charter version 1	15-Aug-2018
Data monitoring committee charter version 2	29-Jan-2019
Data monitoring committee charter version 3	07-Aug-2019
Data monitoring committee charter version 4	11-Jan-2021

A list of members on the data monitoring committee is provided in [Appendix 16.1.4-Section 2](#).

3 Independent Imaging Review (IIR)

Table 3-1 Imaging review charters

Document	Effective Date
Imaging Endpoint Review Charter version 1	15-May-2018
Imaging Endpoint Review Charter version 2	24-May-2018
Imaging Endpoint Review Charter version 3	14-Feb-2019
Imaging Endpoint Review Charter version 4	21-Mar-2019
Imaging Endpoint Review Charter version 5	27-Nov-2019

A list of readers who conducted the independent imaging review is provided in [Appendix 16.1.4-Section 2](#). Summary of reader input tables for PSMA eligibility, RECIST 1.1, PCWG3, Global Subject Level Determination, and Adjudication are included as appendices in the Imaging Endpoint Review Charters.



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ^{177}Lu -PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 1.0

Date: 22 March 2018

IND No.: 133,661 (^{177}Lu -PSMA-617)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ^{177}Lu -PSMA-617

Sponsor: Endocyte, Inc.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: [Name], MB.ChB., BSc., MSc.,
MD., MRCP., FRCR
[Contact]
Endocyte, Inc.
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Page 2 of 87

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Table of Contents

Site Principal Investigator Signature	2
Table of Contents	3
Revision History	7
Clinical Trial Summary.....	8
List of Abbreviations and Definitions.....	10
1. Introduction	12
1.1 Background information.....	12
1.2 Summary of nonclinical studies with clinical significance	16
1.3 Summary of known and potential risks and benefits.....	17
2. Trial Objectives and Endpoints	18
2.1 Trial objectives	18
2.1.1 Primary objective	18
2.1.2 Key secondary objectives.....	18
2.1.3 Additional secondary objectives	18
2.2 Trial endpoints.....	18
2.2.1 Primary endpoint.....	18
2.2.2 Key Secondary endpoints.....	18
2.2.3 Additional Secondary endpoints	19
3. Trial Design	20
3.1 Overview of the clinical trial design	20
3.2 Rationale for the study design	22
3.3 Measures taken to minimize/avoid bias	23
3.4 Description of the clinical trial	23
3.4.1 Description of investigational medicinal product	23
3.4.2 Dosage and rationale for dose selection.....	23
3.4.3 Subject allocation to treatment.....	24
3.4.4 End of treatment visit	24
3.4.5 Duration of Subject Participation.....	24
3.5 End of trial definition	25
4. Selection and Withdrawal of Subjects.....	25
4.1 Inclusion criteria.....	25
4.2 Exclusion criteria.....	27
4.3 Subject withdrawal of consent for study or treatment.....	28
5. Treatment of Subjects	28

5.1	Treatment with the investigational medicinal product	28
5.1.1	Administration of ¹⁷⁷ Lu-PSMA-617	28
5.1.2	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	29
5.1.3	Management of toxicity adverse events: dosing delays and modification.....	29
5.2	Best supportive/best standard of care	31
5.3	Concomitant medications/ supportive care	31
5.3.1	Permitted concomitant medications/ supportive care	31
5.3.2	Prohibited concomitant medications	32
5.4	Monitoring treatment compliance	32
5.5	Treatment discontinuation	32
6.	Study Assessments and Procedures.....	32
6.1	Screening procedures and baseline assessments	32
6.2	Efficacy assessments	34
6.2.1	Radiographic imaging for tumor assessments	35
6.2.2	RECIST criteria.....	35
6.2.3	Symptomatic skeletal events	35
6.2.4	Pain score	35
6.2.5	Health-related quality of life	35
6.2.6	Health Economics	36
6.2.7	Clinical progression	37
6.2.8	PSA levels.....	37
6.3	Safety assessments.....	37
6.3.1	Clinical laboratory evaluations	37
6.3.2	Vital signs	38
6.3.3	Electrocardiograms	38
6.4	End of treatment visit procedures.....	38
6.5	Long-term follow-up procedures.....	38
7.	Adverse Events.....	38
7.1	Adverse event definitions	38
7.2	Evaluating and recording adverse events	39
7.3	Immediate Adverse Event Reporting	40
7.3.1	Serious Adverse Events	40
7.3.2	Serious adverse event subject follow-up.....	40
7.3.3	Sponsor Contact Information for Immediate Reporting	41
8.	Statistics.....	41
8.1	Sample size and power determination	41

8.2	Analysis populations42
8.3	Demographics and baseline disease characteristics42
8.4	Patient disposition42
8.5	Efficacy analyses43
8.5.1	Primary efficacy analysis43
8.5.2	Secondary efficacy analyses43
8.6	Safety analyses44
8.6.1	Extent of exposure44
8.6.2	Analysis of adverse events44
8.6.3	Analysis of laboratory assessments.....	.45
8.6.4	Analysis of vital sign data.....	.45
8.7	Interim analyses.....	.45
8.7.1	Interim efficacy analyses45
8.7.2	Interim safety analyses.....	.45
8.8	Criteria for termination of trial.....	.45
9.	Access to Source Data/Documents.....	.46
10.	Ethics46
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB).....	.46
10.2	Informed consent46
10.3	Health Insurance Portability and Accountability Act.....	.47
10.4	Confidentiality.....	.47
11.	Compliance and quality control.....	.47
11.1	Compliance with Monitoring and Audits47
12.	Data Handling, Record Keeping, and Compliance48
12.1	Investigational medicinal product accountability.....	.48
12.2	Breaking the blind48
12.3	Data collection forms and source document identification48
12.4	Record maintenance and retention49
12.5	Archiving49
13.	Publication Policy.....	.50
14.	References50
Appendix 1	Schedules of Assessments.....	.57
Appendix 2	Suggested treatment guidelines64
Appendix 3	Principal Investigator Signature65

Appendix 4a	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....	66
Appendix 4b	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....	67
Appendix 5	Common Terminology Criteria for Adverse Events.....	68
Appendix 6	Response Evaluation Criteria in Solid Tumors	69
Appendix 7	Prostate Cancer Working Group 3 Recommendations	70
Appendix 8	BPI-SF (<i>sample only, not for patient use</i>)	72
Appendix 9	EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	75
Appendix 10	FACT-P (Functional Assessment of Cancer Therapy – Prostate) (<i>sample only, not for patient use</i>)	79
Appendix 11	PCCTC Bone Scan Assessment Tool.....	83

List of tables

Table 1	Toxicity management and dose modification recommendations.....	30
Table 2	Screening procedures and baseline assessments	33
Table 3	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1).....	58
Table 4	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)	59
Table 5	Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)	
	61	
Table 6	Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....	62

List of figures

Figure 1	Diagram of trial design	21
----------	-------------------------------	----

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>A long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (\pm1 month) via phone, email, or letter for 24 months or until the the overall censoring rate for survival reduces to a level identified in the SAP.</p> <p>An End of Treatment visit should occur once a patient is to enter the long term follow up. This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 750 patients.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.

Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (± 1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	There will be 2 interim analyses to evaluate if the trial should be stopped early for efficacy. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation	Term/Definition
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved

agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#), [Cheng et al 2015](#), [Badrising et al 2014](#), [Brasso et al 2015](#), [Loriot et al 2013](#), [Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#), [Ghosh and Heston 2004](#), [Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al 2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium-energy β -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile

and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of \geq 6 GBq/160 mCi are given.

Hofman (2017) presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2017](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 85% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 57% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 43% had a reduction of PSA of 80% or more. In 17 patients with measurable disease, the overall response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 71% (complete response [CR] and partial response [PR]). Median overall survival was 12.7 months. These safety and efficacy data also translated into significantly improved quality of life scores in 37% and reduction in pain scores in 43% of subjects.

In summary, over 20 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series have confirmed 8% incidence of Grade 1 to 2 xerostomia, less than 10% asymptomatic hematological of Grade 3 to 4 toxicity and no significant renal toxicity. Efficacy has been demonstrated on multiple clinically

significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADS and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface area of 1.7 m^2 . However, considering that a more intensive dosing schedule was tested in rats, relative to the

proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2017). In the trial, 30 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The incidence of drug related Grade 3 or 4 neutropenia, anemia and thrombocytopenia were 7%, 7% and 13% respectively. The only other Grade 3 or 4 drug related toxicity were Grade 3 fatigue and bone pain in 3% of patients.

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu -PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. Radiographic progression-free survival (rPFS)
2. RECIST response to include:
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
3. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ^{177}Lu -PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Primary endpoint

The primary endpoint is OS and is defined as the time from randomization to the date of death from any cause.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. Radiographic progression-free survival (rPFS) defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate

Cancer Working Group 3 (PCWG3) Guidelines ([Scher et al 2016](#)) or death from any cause.

2. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
3. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ^{177}Lu -PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

Page 20 of 87

- c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

- a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

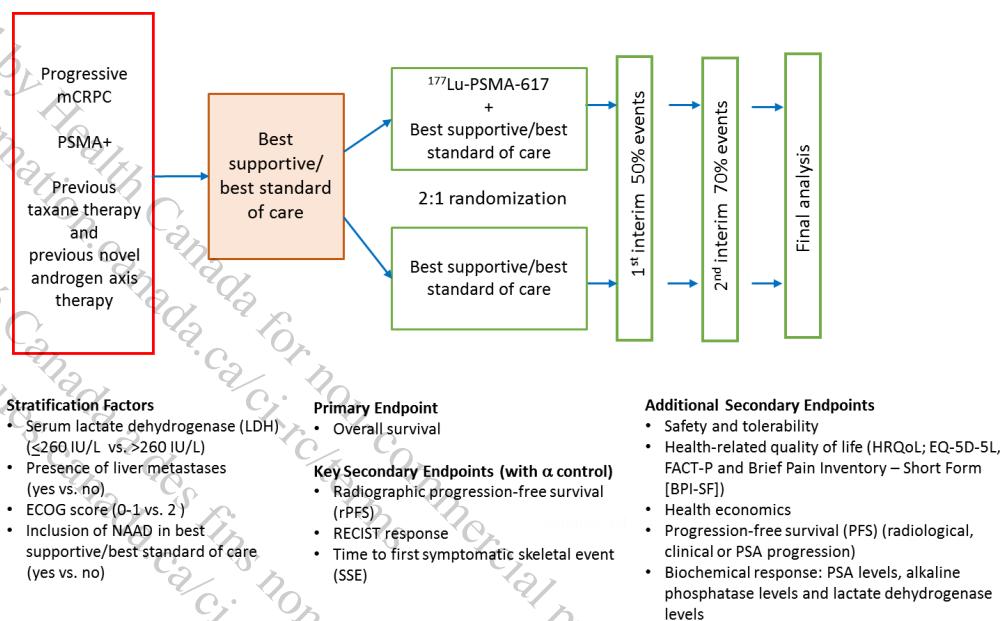


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ⁶⁸Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ¹⁷⁷Lu-PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the treatment part of the study at any time. If a patient withdraws consent for the treatment part of the study, the patient will continue to be followed for long term follow up unless they specifically withdraw for the long term follow up of the study.

An End of Treatment (EOT) visit should occur once a patient is to enter the long-term follow-up part of the study. This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (± 1 month) via phone, email, or letter for 24 months or until the overall censoring rate for survival reduces to a level identified in the statistical analysis plan (SAP).

This study will enroll approximately 750 patients involving about 80 sites worldwide.

3.2 Rationale for the study design

The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu -PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ¹⁷⁷Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ¹⁷⁷Lu-PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

¹⁷⁷Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2017).

Clinical series now show reports of more than 4 cycles of ¹⁷⁷Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018). In addition, a recent review suggests optimal dosing of 6 cycles of ¹⁷⁷Lu-PSMA-617 administered every 6 weeks in a

decreasing scale reaching a total cumulative absorbed dose of 44 GBq ([Emmett et al 2017](#)). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ¹⁷⁷Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ¹⁷⁷Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ¹⁷⁷Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient is to enter the long term follow up part of the study. This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period.

Total duration of the trial for randomized patients is expected to be 19 to 23 months, including a 1-month screening period, 6 to 10-month treatment period and a long-term follow-up period lasting 24 months or at least until the overall censoring rate for survival reduces to a level identified in the SAP.

Total duration of the study, from first date of randomization to last follow-up, will be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue for approximately 38 months or until the overall censoring rate for survival reduces to a level identified in the SAP.

For timing of the 2 formal interim analyses and any rules for early statistical curtailment, refer to Section 8.7 and Section 8.8.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. Participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga -PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have prior orchiectomy and/or ongoing androgen-deprivation therapy and a castrate level of serum testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient is not willing to receive a second taxane regimen, or

Page 26 of 87

- b. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation or intolerance).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesion(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
 - a. Bone marrow reserve:
 - White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
 - Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
 - Hemoglobin ≥ 9 g/dL (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)
 - b. Hepatic:
 - Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases
 - c. Renal:
 - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min
15. Albumin > 3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)

16. Patients on a stable bisphosphonate or denosumab regimen for ≥30 days prior to randomization are eligible.
17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

For patients who have partners of childbearing potential:

18. Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 3 months after last study drug administration.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 or hemi-body irradiation within 6 months prior to randomization. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion within 30 days of randomization.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active

hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.

11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with adequately treated non-melanoma skin cancer, superficial bladder cancer and patients with prior history of malignancy who have been disease free for more than 3 years are eligible.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient only withdraws consent for the treatment part of the study, the patient will continue to be followed for long-term follow-up unless he also specifically withdraws from the long-term follow-up period.

This trial design is intent to treat so that all subjects will be followed for approximately 24 months or until the overall censoring rate for survival reduces to a level identified in the SAP.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by the intravenous route through an indwelling catheter and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15 minutes before and at 30 and 60 minutes following injection.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 15 business days prior to the planned administration for each cycle.

5.1.2 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.3 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

- If a treatment delay persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count <3.0 × 10⁹/L• ANC <1.5 × 10⁹/L	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of < 75 × 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates can be stopped or started at the discretion of the investigator throughout the study.

Patients must remain castrate and receive a luteinizing hormone-releasing hormone analogue (agonist or antagonist) or polyestradiol phosphate throughout the study.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include: corticosteroids, antiandrogens, or ketoconazole.

Local external beam radiotherapy, including palliative external radiation is allowed.

Supportive care should be provided as deemed necessary by the treating physician.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.3 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging

done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.3 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.4 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.5 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)).

This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL Group 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being (Cella et al 1993). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies (Cella et al 1993, Esper et al 1997)
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format (Webster et al 2003)

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.6 Health Economics

A health economics (HE) sub-study will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.7 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.8 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

- | | | | |
|------------|--|--|---|
| Chemistry | <ul style="list-style-type: none">• sodium• potassium• total and direct bilirubin• ALP• AST• ALT | <ul style="list-style-type: none">• LDH• blood urea nitrogen• creatinine• uric acid• phosphorus• chloride | <ul style="list-style-type: none">• bicarbonate• calcium• glucose• total protein• albumin |
| Urinalysis | <ul style="list-style-type: none">• urine pH• protein content• specific gravity• appearance and color | <ul style="list-style-type: none">• glucose• ketones | |
| Hematology | <ul style="list-style-type: none">• complete blood count (white blood cell count and differential)• red blood cell count• hemoglobin• hematocrit• platelet count | | |

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect AE assessments, and survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study will be asked for permission to continue long-term status updates.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	<p>Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p>
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death;• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p>
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All adverse events (AEs) will be graded according to CTCAE v5.0.

AE monitoring for treatment-emergent ⁶⁸Ga-PSMA-11 events will begin with the administration of ⁶⁸GA-PSMA-11 and continue for a period of at least 6 days and will continue up to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and up to Cycle 1 Day 1 for the best supportive/best standard of care-only arm. AE monitoring for treatment-emergent ¹⁷⁷Lu-PSMA-617 events will commence with initial dosing of ¹⁷⁷Lu-PSMA-617 and continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617. AE monitoring for the best supportive/best standard of care-only arm will commence with Cycle 1 Day 1 and continue up to and including 30 days after the last dose of best supportive/best standard of care.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11 and/or

¹⁷⁷Lu-PSMA-617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is “unknown and of questionable relationship to the study drug” the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is “unknown but not related to the study drug” the determination and rationale will be documented in the patient’s case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was

initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

All statistical analyses will be carried out using SAS version 9.3 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Sample size and power determination

The sample size was determined based on the primary endpoint: overall survival. Planned enrollment for this study is approximately 750 subjects.

Under the null hypothesis, median survival is assumed to be 10 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Based on a non-linear patient accrual profile over 13 months and a follow up of 24 months (or until the the overall censoring rate for survival reduces to a level identified in the SAP), a total of 750 patients randomized will yield 489 events.

With two interim analyses at 50% (243/489, expected approximately 16.5 months after first patient randomized) and 70% (344/489, expected approximately 20.5 months after first patient randomized) events with adjusted 1-sided p-values of 0.00153 and 0.00690 respectively and a 1-

sided p-value in the final analysis of 0.02266, this trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.

The observed HRs that will meet the stated p-value thresholds at the first and second interim analyses, and at the final analysis, are 0.669, 0.754 and 0.825, respectively (corresponding to 4.9-month, 3.3-month, and 2.1 month increases in median overall survival assuming median OS on best supportive/best standard of care of 10 months). The cumulative probabilities of stopping at the first and second interims under the alternative hypothesis are 35.4% and 61.3% respectively.

8.2 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. Patient efficacy data in this dataset will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.3 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.4 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.5 Efficacy analyses

8.5.1 Primary efficacy analysis

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause.

Patients who are lost to follow-up or are alive at the time of analysis will be censored at the time they were last known to be alive or at the date of event cut-off for OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

A stratified Cox proportional hazards regression model will be used to analyze OS in the FAS dataset. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors. The HR (active: control), its 95% confidence interval, and the associated 2-sided p-value will be presented. A supportive analysis will be provided via a stratified log-rank test, stratifying again for the randomization stratification factors.

8.5.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. rPFS
2. RECIST ORR and DCR
3. Time to SSE

Time to SSE and rPFS will be analyzed using a Cox regression model in the same manner as described for the primary endpoint. Objective response and disease control rate will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoints will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if the primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure. This procedure is reasonable given the positive correlation between the 3 key secondary endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints are:

1. To evaluate the safety and tolerability of ^{177}Lu -PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.

3. Health economics
4. PFS is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints will be analyzed using a Cox regression model in the same manner as described for the primary endpoint. Disease control rate DCR will be analyzed in the same manner as objective response rate and HRQoL will be analyzed in the same manner as pain score over time. Time to pain response will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.6 Safety analyses

8.6.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.6.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga -PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga -PSMA-11 but appeared following dosing, or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of the first dose of ^{68}Ga -PSMA-11 up to 6 days after the date of the initial dose of ^{68}Ga -PSMA-11 or the first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm.

A ^{177}Lu -PSMA-617 TEAE is defined as an AE that was not present prior to treatment with ^{177}Lu -PSMA-617 but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the date of the first dose of ^{177}Lu -PSMA-617 up to 30 days after the date of the last dose of

¹⁷⁷Lu-PSMA-617 or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.6.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.6.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.7 Interim analyses

8.7.1 Interim efficacy analyses

As described above in Section 8.1, two formal interim efficacy analyses are planned at 50% and 70% of the total planned number of events. The purpose of these interim analyses is to allow early stopping for efficacy should sufficient statistical evidence be found to reject the null hypothesis of no survival effect. There will be no assessment for futility.

These interim analyses will be overseen by a fully Independent Data Monitoring Committee (IDMC) who may recommend stopping the study for superior efficacy at the first or second interim if the corresponding pre-specified 1-sided p-value threshold is met. An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any interim analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision to continue or stop the trial based on either interim analysis.

8.7.2 Interim safety analyses

Safety monitoring interim analyses will be conducted quarterly by the IDMC. These analyses will commence following the completion of the first three months of study accrual.

8.8 Criteria for termination of trial

Safety data will be reviewed on an ongoing basis by an IDMC who will provide recommendations as necessary to the sponsor regarding the ongoing conduct of the study. The trial may also be terminated due to an early stop due to efficacy, completion of study enrollment and treatment/follow up.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and

Page 47 of 87

that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study.

with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmadzadehfar et al 2016

Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget*. 2016;7(11):12477-88.

Ahmadzadehfar et al 2015

Ahmadzadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with 177Lu-DKFZ-617-PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research*. 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015; 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med*. 2015;56(6):914-20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic

Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. European urology. 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256-61.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy-Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. Value Health. 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. Prostate Cancer Prostatic Dis. 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. Nucl Med Biol. 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials. 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. *J Nucl Med.* 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. *Cancer Med.* 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem.* 2004;91:528–39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. *Clin Cancer Res.* 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Res.* 2009;69(17), 6932–40.

Hofman et al 2017

Hofman MS, Sandhu S, Eu P, Price J, Akhurst T, Iravani A, et al. Lutetium-177 PSMA (LuPSMA) theranostics phase II trial: Efficacy, safety and QoL in patients with castrate-resistant prostate cancer treated with LuPSMA. [abstract/presentation] In 2017 European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain. *Ann Oncol* 2017; 28 (suppl_5):v269-v294.

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract.* 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016 Oct;57(Suppl 3):97S-104S.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]-Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(6):987–88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of Oncology* 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013;24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXNN Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate

Page 55 of 87

resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 56 of 87

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. 177Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 57 of 87

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review		X-----		X-----		
AE monitoring ^a		X-----		X-----		
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit.					

^a Adverse event monitoring for treatment-emergent ^{177}Lu -PSMA-617 events will commence with initial dosing of ^{177}Lu -PSMA-617

^b Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01

Version no.: 1.0

Endocyte, Inc.

22 March 2018

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6*	End of Treatment ^g	Long-term follow-up
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^c					X ^a	X ^a	X	
AE monitoring ^b	X					X ^a	X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{g,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	
Serum testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the end of treatment visit								

Protocol no. PSMA-617-01
Version no. 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

* After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone.

- ^a Phone evaluation is allowed during Weeks 2, 4, and 6.
- ^b Adverse event monitoring for treatment-emergent ^{177}Lu -PSMA-617 events will commence with initial dosing of ^{177}Lu -PSMA-617 and continue up to and including 30 days after the last dose of ^{177}Lu -PSMA-617.
- ^c Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 28.
- ^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 minutes before, 30 minutes post, and 60 minutes post ^{177}Lu -PSMA-617 administration.
- ^e To be completed prior to drug administration (if applicable) on Day 1.
- ^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (± 1 week). If at any time, WBC count $<3.0 \times 10^9/\text{L}$, ANC is $<1.5 \times 10^9/\text{L}$, platelet count is $<100 \times 10^9/\text{L}$ or hemoglobin level is $<9 \text{ g/dL}$, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a \geq Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.
- ^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study
- ^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5. Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will begin Cycle 1 Day 1

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Table 6. Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6						After Cycle 6	End of Treatment ^f	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 8 weeks (± 1 week)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^a						X ^a	X	
AE monitoring	X						X ^a	X	
Weight	X ^b						X ^b	X	
ECOG	X ^b						X ^b	X	
Directed physical exam	X ^b						X ^b	X	
Vital signs ^c	X ^b						X ^b	X	
EQ-5D-5L	X ^{d,g}						X ^{d,g}	X ^{d,g}	
FACT-P	X ^{d,g}						X ^{d,g}	X ^{d,g}	
BPI-SF	X ^{d,g}						X ^{d,g}	X	
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology ^e	X ^b		X ^b		X ^b		X ^b	X	
Chemistry ^e	X ^b		X ^b		X ^b		X ^b	X	
Serum testosterone	X ^b						X ^b	X	
PSA	X ^b						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

^a Phone evaluation is allowed during Weeks 2, 4, and 6.

^b Within 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.

Protocol no. PSMA-617-01
Version no. 1.0

Endocyte, Inc.
22 March 2018

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- ^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1).
- ^d To be completed prior to drug administration (if applicable) on Day 1.
- ^e For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (\pm 1 week). If at any time, WBC $<3.0 \times 10^9/L$, ANC is $<1.5 \times 10^9/L$, platelet count is $<100 \times 10^9/L$ or hemoglobin level is <9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.
- ^f To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
- ^g HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Page 65 of 87

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramidate. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 68 of 87

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Page 69 of 87

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">Record outcome as new lesions, no new lesions or resolved lesionFirst scheduled reassessment:<ul style="list-style-type: none">No new lesions: continue therapyNew lesions: perform a confirmatory scan 6 or more weeks laterConfirmatory scan:<ul style="list-style-type: none">No new lesions: continue therapyAdditional new lesions: progressionSubsequent scheduled reassessments:<ul style="list-style-type: none">No new lesions: continueNew lesions: progressionChanges in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">Exclude pseudoprogression in the absence of symptoms or other signs of progressionAt least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documentedFor scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scanDate of progression is the date of the scan that first documents the second lesionChanges in intensity of uptake alone do not constitute either progression or regressionReport the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to [Scher et al 2016](#) for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 72 of 87

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Page 73 of 87

Brief Pain Inventory (Short Form)

Time: ___ : ___ AM PM

Today's Date (day, month, year):

Day - **Month** (day, month, year).

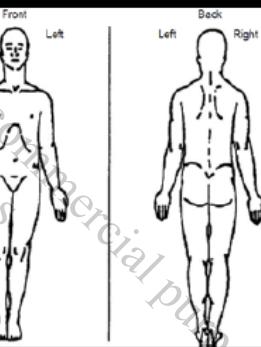
JAN	JAN	MAR	MAY	JUL	SEP	NOV
FEB	FEB	APR	JUN	AUG	OCT	DEC
Day	Year					

- Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.



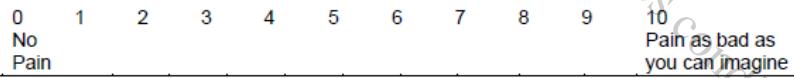
4. Please rate your pain by circling the one number that best describes your pain at its [least] in the last 24 hours.



5. Please rate your pain by circling the one number that best describes your pain on the average.



6. Please rate your pain by circling the one number that best describes how much pain you have right now.



Copyright 1991 Charles S. Cleland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Page 74 of 87

Today's Date (Day, Month, Year): <u> </u> - <u> </u> - <u> </u> (Example: 08-FEB-2016) <u> </u> DAY <u> </u> MONTH <u> </u> YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Page 75 of 87

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (sample only, not for patient use)

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Page 76 of 87



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT

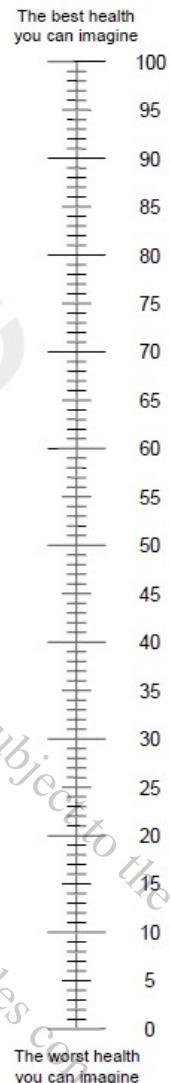
- I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Page 79 of 87

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy -
Prostate) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 83 of 87

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 1.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

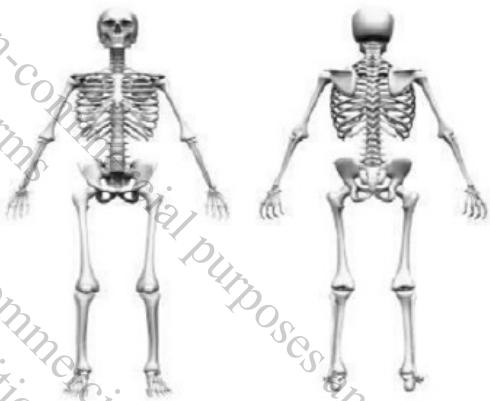
Endocyte, Inc.
22 March 2018

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

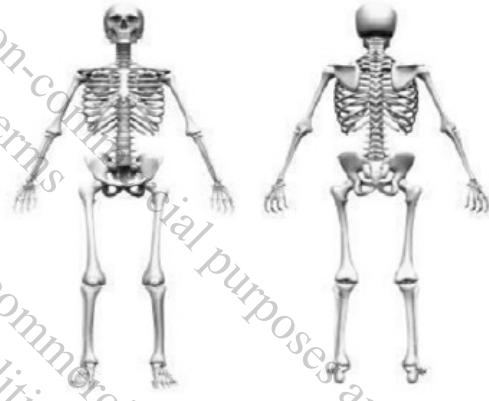
Page 85 of 87

Week 8 BASELINE Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening:	Draw site(s) of NEW lesion(s) on skeleton:  <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
<i>* Presence of new lesions at this time does not confirm progression</i>	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

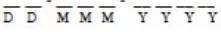
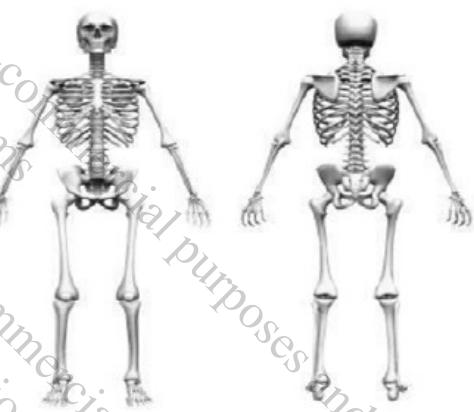
Page 86 of 87

Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan:	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 87 of 87

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 42.0

Date: 22 March 2018 16 January 2019

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)
133.925 or site equivalent (⁶⁸Ga-PSMA-11)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617; ⁶⁸Ga-PSMA-11

Sponsor: Endocyte, Inc.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: [Name], MB, ChB, BSc,
Richard Messmann, MD, MHS, MSc,
MD, MRCP, FRCR
[Contact]
Vice President, Medical [Contact] Affairs
Endocyte, Inc.
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Page 2 of 96

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

| Protocol No./Acronym: *from Title page*
Version No.: *from Title page*

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
20 March December 2018

Page 3 of 96

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Table of Contents

<u>Site Principal Investigator Signature</u>	3
<u>Table of Contents</u>	4
<u>Revision History</u>	12
<u>Clinical Trial Summary</u>	13
<u>List of Abbreviations and Definitions</u>	15
<u>1. Introduction</u>	17
<u>1.1 Background information</u>	17
<u>1.2 Summary of nonclinical studies with clinical significance</u>	21
<u>1.3 Summary of known and potential risks and benefits</u>	21
<u>2. Trial Objectives and Endpoints</u>	22
<u>2.1 Trial objectives</u>	22
<u>2.1.1 Primary objective</u>	22
<u>2.1.2 Key secondary objectives</u>	22
<u>2.1.3 Additional secondary objectives</u>	23
<u>2.2 Trial endpoints</u>	23
<u>2.2.1 Primary endpoint</u>	23
<u>2.2.2 Key Secondary endpoints</u>	23
<u>2.2.3 Additional Secondary endpoints</u>	24
<u>3. Trial Design</u>	25
<u>3.1 Overview of the clinical trial design</u>	25
<u>3.2 Rationale for the study design</u>	28
<u>3.3 Measures taken to minimize/avoid bias</u>	28
<u>3.4 Description of the clinical trial</u>	28
<u>3.4.1 Description of investigational medicinal product</u>	28
<u>3.4.2 Dosage and rationale for dose selection</u>	29
<u>3.4.3 Subject allocation to treatment</u>	30
<u>3.4.4 End of treatment visit</u>	30
<u>3.4.5 Duration of Subject Participation</u>	30
<u>3.5 End of trial definition</u>	30
<u>4. Selection and Withdrawal of Subjects</u>	31
<u>4.1 Inclusion criteria</u>	31
<u>4.2 Exclusion criteria</u>	33
<u>4.3 Subject withdrawal of consent for study or treatment</u>	34
<u>5. Treatment of Subjects</u>	34
<u>5.1 Treatment with the investigational medicinal product</u>	34
<u>5.1.1 Administration of ¹⁷⁷Lu PSMA-617</u>	34

Page 5 of 96

5.1.2	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu PSMA-617 injections	35
5.1.3	Management of toxicity adverse events; dosing delays and modification	35
5.2	Best supportive/best standard of care	37
5.3	Concomitant medications/ supportive care	37
5.3.1	Permitted concomitant medications/ supportive care	37
5.3.2	Prohibited concomitant medications	38
5.4	Monitoring treatment compliance	39
5.5	Treatment discontinuation	39
6.	Study Assessments and Procedures	39
6.1	Screening procedures and baseline assessments	39
6.2	Efficacy assessments	41
6.2.1	Radiographic imaging for tumor assessments	41
6.2.2	RECIST criteria	42
6.2.3	Symptomatic skeletal events	42
6.2.4	Pain score	42
6.2.5	Health related quality of life	42
6.2.6	Health Economics	43
6.2.7	Clinical progression	43
6.2.8	PSA levels	44
6.3	Safety assessments	44
6.3.1	Clinical laboratory evaluations	44
6.3.2	Vital signs	44
6.3.3	Electrocardiograms	44
6.4	End of treatment visit procedures	45
6.5	Long-term follow up procedures	45
7.	Adverse Events	45
7.1	Adverse event definitions	45
7.2	Evaluating and recording adverse events	46
7.3	Immediate Adverse Event Reporting	46
7.3.1	Serious Adverse Events	46
7.3.2	Serious adverse event subject follow up	47
7.3.3	Sponsor Contact Information for Immediate Reporting	47
8.	Statistics	47
8.1	Sample size and power determination	48
8.2	Analysis populations	49
8.3	Demographics and baseline disease characteristics	49
8.4	Patient disposition	49
8.5	Efficacy analyses	49

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018/16 January 2019

Page 6 of 96

8.5.1 Primary efficacy analysis	49
8.5.2 Secondary efficacy analyses	51
8.6 Safety analyses	52
8.6.1 Extent of exposure	52
8.6.2 Analysis of adverse events	52
8.6.3 Analysis of laboratory assessments	52
8.6.4 Analysis of vital sign data	53
8.7 Interim analyses	53
8.7.1 Interim efficacy analyses	53
8.7.2 Interim safety analyses	53
8.8 Criteria for termination of trial	53
9 Access to Source Data Documents	54
10 Ethics	54
10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	54
10.2 Informed consent	54
10.3 Health Insurance Portability and Accountability Act	55
10.4 Confidentiality	55
11 Compliance and quality control	55
11.1 Compliance with Monitoring and Audits	55
12 Data Handling, Record Keeping, and Compliance	56
12.1 Investigational medicinal product accountability	56
12.2 Breaking the blind	56
12.3 Data collection forms and source document identification	56
12.4 Record maintenance and retention	57
12.5 Archiving	57
13 Publication Policy	57
14 References	59
Appendix 1 Schedules of Assessments	65
Appendix 2 Suggested treatment guidelines	72
Appendix 3 Principal Investigator Signature	73
Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	74
Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	75
Appendix 5 Common Terminology Criteria for Adverse Events	76
Appendix 6 Response Evaluation Criteria in Solid Tumors	77
Appendix 7 Prostate Cancer Working Group 3 Recommendations	78

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018/16 January 2019

Page 7 of 96

<u>Appendix 8</u>	<u>BPI SF (sample only, not for patient use)</u>	80
<u>Appendix 9</u>	<u>EQ 5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (sample only, not for patient use)</u>	83
<u>Appendix 10</u>	<u>FACT P (Functional Assessment of Cancer Therapy - Prostate) (sample only, not for patient use)</u>	87
<u>Appendix 11</u>	<u>PCCTC Bone Scan Assessment Tool</u>	91
<u>Site Principal Investigator Signature</u>		3
<u>Table of Contents</u>		4
<u>Revision History</u>		12
<u>Clinical Trial Summary</u>		13
<u>List of Abbreviations and Definitions</u>		15
<u>1.</u>	<u>Introduction</u>	17
<u>1.1</u>	<u>Background information</u>	17
<u>1.2</u>	<u>Summary of nonclinical studies with clinical significance</u>	21
<u>1.3</u>	<u>Summary of known and potential risks and benefits</u>	21
<u>2.</u>	<u>Trial Objectives and Endpoints</u>	22
<u>2.1</u>	<u>Trial objectives</u>	22
<u>2.1.1</u>	<u>Primary objective</u>	22
<u>2.1.2</u>	<u>Key secondary objectives</u>	22
<u>2.1.3</u>	<u>Additional secondary objectives</u>	23
<u>2.2</u>	<u>Trial endpoints</u>	23
<u>2.2.1</u>	<u>Alternate Primary endpoints</u>	23
<u>2.2.2</u>	<u>Key Secondary endpoints</u>	23
<u>2.2.3</u>	<u>Additional Secondary endpoints</u>	24
<u>3.</u>	<u>Trial Design</u>	25
<u>3.1</u>	<u>Overview of the clinical trial design</u>	25
<u>3.2</u>	<u>Rationale for the study design</u>	28
<u>3.3</u>	<u>Measures taken to minimize/avoid bias</u>	28
<u>3.4</u>	<u>Description of the clinical trial</u>	28
<u>3.4.1</u>	<u>Description of investigational medicinal product</u>	28
<u>3.4.2</u>	<u>Dosage and rationale for dose selection</u>	29
<u>3.4.3</u>	<u>Subject allocation to treatment</u>	30
<u>3.4.4</u>	<u>End of treatment visit</u>	30
<u>3.4.5</u>	<u>Duration of Subject Participation</u>	30
<u>3.5</u>	<u>End of trial definition</u>	30
<u>4.</u>	<u>Selection and Withdrawal of Subjects</u>	31
<u>4.1</u>	<u>Inclusion criteria</u>	31
<u>4.2</u>	<u>Exclusion criteria</u>	33

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018/16 January 2019

Page 8 of 96

4.3	Subject withdrawal of consent for study or treatment	34
5.	Treatment of Subjects	34
5.1	Treatment with the investigational medicinal product.....	34
5.1.1	Administration of ⁶⁸ Ga-PSMA-11.....	34
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-617	34
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	35
5.1.4	Management of toxicity adverse events: dosing delays and modification	35
5.2	Best supportive/best standard of care	37
5.3	Concomitant medications/ supportive care	38
5.3.1	Permitted concomitant medications/ supportive care	38
5.3.2	Prohibited concomitant medications	38
5.4	Monitoring treatment compliance	39
5.5	Treatment discontinuation	39
6.	Study Assessments and Procedures	39
6.1	Screening procedures and baseline assessments	39
6.2	Efficacy assessments.....	41
6.2.1	Radiographic imaging for tumor assessments.....	41
6.2.2	RECIST criteria.....	42
6.2.3	Symptomatic skeletal events	42
6.2.4	Pain score	42
6.2.5	Health-related quality of life	42
6.2.6	Health Economics	43
6.2.7	Clinical progression.....	43
6.2.8	PSA levels	44
6.3	Safety assessments	44
6.3.1	Clinical laboratory evaluations.....	44
6.3.2	Vital signs.....	44
6.3.3	Electrocardiograms.....	44
6.3.4	Birth Control	44
6.4	End of treatment visit procedures	45
6.5	Long-term follow-up procedures	45
7.	Adverse Events	45
7.1	Adverse event definitions	45
7.2	Evaluating and recording adverse events.....	46
7.3	Immediate Adverse Event Reporting	46
7.3.1	Serious Adverse Events.....	46
7.3.2	Serious adverse event subject follow-up	47
7.3.3	Sponsor Contact Information for Immediate Reporting.....	47

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22-March-2018-16 January 2019

Page 9 of 96

<u>8.</u>	<u>Statistics</u>	<u>47</u>
<u>8.1</u>	<u>Sample size and power determination</u>	<u>48</u>
<u>8.2</u>	<u>Analysis populations.....</u>	<u>49</u>
<u>8.3</u>	<u>Demographics and baseline disease characteristics</u>	<u>49</u>
<u>8.4</u>	<u>Patient disposition.....</u>	<u>49</u>
<u>8.5</u>	<u>Efficacy analyses</u>	<u>49</u>
<u>8.5.1</u>	<u>Alternate primary endpoint efficacy analysis.....</u>	<u>49</u>
<u>8.5.2</u>	<u>Secondary efficacy analyses.....</u>	<u>51</u>
<u>8.6</u>	<u>Safety analyses.....</u>	<u>52</u>
<u>8.6.1</u>	<u>Extent of exposure.....</u>	<u>52</u>
<u>8.6.2</u>	<u>Analysis of adverse events</u>	<u>52</u>
<u>8.6.3</u>	<u>Analysis of laboratory assessments.....</u>	<u>52</u>
<u>8.6.4</u>	<u>Analysis of vital sign data</u>	<u>53</u>
<u>8.7</u>	<u>IDMC and Interim Data Evaluation.....</u>	<u>53</u>
<u>8.7.1</u>	<u>IDMC</u>	<u>53</u>
<u>8.7.2</u>	<u>Formal Interim Analysis of OS</u>	<u>54</u>
<u>9.</u>	<u>Access to Source Data/Documents</u>	<u>54</u>
<u>10.</u>	<u>Ethics</u>	<u>54</u>
<u>10.1</u>	<u>Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)</u>	<u>54</u>
<u>10.2</u>	<u>Informed consent</u>	<u>54</u>
<u>10.3</u>	<u>Health Insurance Portability and Accountability Act.....</u>	<u>55</u>
<u>10.4</u>	<u>Confidentiality.....</u>	<u>55</u>
<u>11.</u>	<u>Compliance and quality control</u>	<u>55</u>
<u>11.1</u>	<u>Compliance with Monitoring and Audits</u>	<u>55</u>
<u>12.</u>	<u>Data Handling, Record Keeping, and Compliance</u>	<u>56</u>
<u>12.1</u>	<u>Investigational medicinal product accountability.....</u>	<u>56</u>
<u>12.2</u>	<u>Breaking the blind</u>	<u>56</u>
<u>12.3</u>	<u>Data collection forms and source document identification</u>	<u>56</u>
<u>12.4</u>	<u>Record maintenance and retention</u>	<u>57</u>
<u>12.5</u>	<u>Archiving</u>	<u>57</u>
<u>13.</u>	<u>Publication Policy.....</u>	<u>57</u>
<u>14.</u>	<u>References</u>	<u>59</u>
<u>Appendix 1</u>	<u>Schedules of Assessments</u>	<u>65</u>
<u>Appendix 2</u>	<u>Suggested treatment guidelines</u>	<u>72</u>
<u>Appendix 3</u>	<u>Principal Investigator Signature</u>	<u>73</u>
<u>Appendix 4a</u>	<u>Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	<u>74</u>

Protocol no. PSMA-617-01

Version no.: 42.0

Endocyte, Inc.

22-March-2018-16 January 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 10 of 96

<u>Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	75
<u>Appendix 5 Common Terminology Criteria for Adverse Events</u>	76
<u>Appendix 6 Response Evaluation Criteria in Solid Tumors</u>	77
<u>Appendix 7 Prostate Cancer Working Group 3 Recommendations.....</u>	78
<u>Appendix 8 BPI-SF (sample only, not for patient use).....</u>	80
<u>Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (sample only, not for patient use)</u>	83
<u>Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (sample only, not for patient use)</u>	87
<u>Appendix 11 PCCTC Bone Scan Assessment Tool.....</u>	91

List of tables

<u>Table 1 Toxicity management and dose modification recommendations</u>	36
<u>Table 2 Screening procedures and baseline assessments</u>	39
<u>Table 3 Schedule of assessments: ^{177}Lu PSMA-617 plus best supportive/best standard of care arm (Cycle 1)</u>	66
<u>Table 4 Schedule of assessments: ^{177}Lu PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....</u>	67
<u>Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	69
<u>Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	70
<u>Table 1 Toxicity management and dose modification recommendations</u>	36
<u>Table 2 Screening procedures and baseline assessments</u>	39
<u>Table 3 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)</u>	66
<u>Table 4 Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....</u>	67
<u>Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	69
<u>Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	70

List of figures

<u>Figure 1 Diagram of trial design</u>	26
---	----

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018/16 January 2019

Page 11 of 96

Figure 1 Diagram of trial design..... 26

Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 12 of 96

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	<u>GB only amendment:</u> <u>AE assessment timing to start from consent.</u> <u>Added wording regarding birth control</u>
1.2	26 September 2018	<u>DE only amendment:</u> <u>AE assessment timing to start from consent.</u> <u>Added wording regarding birth control</u>
2.0	16 January 2019	<u>Incorporated GB and DE only amendment changes.</u> <u>Added statement of compliance as required by Sweden.</u> <u>Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis.</u> <u>Clarified inclusion of and timing of start for best supportive/best standard of care.</u> <u>Clarified inclusion/exclusion criteria.</u> <u>Clarified procedures and timing</u> <u>Clarified progression of disease is not considered an AE or SAE.</u> <u>Clarified start and end timing for ⁶⁸Ga-PSMA-11 TEAEs, ¹⁷⁷Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.</u>

Page 13 of 96

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare the two alternative primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>A long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (\pm1 month) via phone, email, or letter for 24 months or until the the overall censoring rate for survival reduces to a level identified in the SAP up to 24 months or until 489 deaths have occurred. An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>An End of Treatment visit should occur once a patient is to enter the long term follow up. This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care, (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 750 patients.</p>

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 14 of 96

Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured <u>within</u> 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (<u>within</u> 3 days prior to each time point) and <u>within</u> 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (± 1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	There will be <u>2 interim analyses to evaluate if 1 analysis at the trial shouldtime of 457 rPFS events where rPFS and OS will be stopped early evaluated for efficacy, followed by a final analysis of OS when 489 OS events have occurred.</u> This trial has <u>90 at least 91.5% overall power and an overall Type I error rate of at most 0.025 1-sided.</u>
Duration of Study:	Total duration of the study will be approximately 38 months.

Page 15 of 96

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DO.R	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 16 of 96

Abbreviation	Term/Definition
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

Page 17 of 96

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved

Page 18 of 96

agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#),[Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#),[Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#),[Cheng et al 2015](#),[Badrising et al 2014](#),[Brasso et al 2015](#),[Loriot et al 2013](#),[Noonan et al 2013](#)),[Azad et al 2015](#),[Cheng et al 2015](#),[Badrising et al 2014](#),[Brasso et al 2015](#),[Loriot et al 2013](#),[Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#),[Ghosh and Heston 2004](#),[Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al 2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity

Page 19 of 96

ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium - energy β - emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β - range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to

Page 20 of 96

salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)
[Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥ 6 GBq/160 mCi are given.

| Hofman ([2017](#)) presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

| Of the screened patients, [85.70%](#) were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 57% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 43% had a reduction of PSA of 80% or more. In 17 patients with measurable disease, the [overall objective](#) response rate [in measurable disease](#) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was [71.82%](#) (complete response [CR] and partial response [PR]). Median overall survival was [12.7–13.5](#) months. These safety and efficacy data also translated into significantly improved quality of life scores [in 37%](#) and reduction in pain scores [in 43% of subjects](#).

In summary, over 20 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series have confirmed 8% incidence of Grade 1 to 2 xerostomia, less than 10% asymptomatic hematological of Grade 3 to 4 toxicity and no significant renal toxicity. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ^{177}Lu -PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

Page 21 of 96

This Phase 3 study will assess the efficacy of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ^{177}Lu -PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ^{177}Lu -PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 μg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 μg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 μg . Using the NOAEL for repeat dosing of PSMA-617 of 400 $\mu\text{g}/\text{kg}$ in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface area of 1.7 m^2 . However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ^{177}Lu -PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al

Page 22 of 96

[2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Fendler et al 2017](#)

[Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44\(6\):1014-1024.](#)

[Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017Yadav et al 2017\).](#)

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation ([Delker et al 2016](#)). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports ([Rahbar et al 2017Rahbar et al 2017](#)).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 ([Hofman et al 2017](#)).[Hofman et al 2018](#). In the trial, 30 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. [The most common treatment-related AE was Grade 1 dry mouth, recorded in 87% of patients.](#) The incidence of drug related Grade 3 or 4 neutropenia, anemia and thrombocytopenia were 7%, [713%](#) and 13% respectively. The only other Grade 3 or 4 drug related toxicity were Grade 3 [fatiguelymphocytopenia](#) and [bone pain in 37% and 34%, respectively,](#) of patients.

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare [the two alternative endpoints of radiographic progression free survival \(rPFS\) and](#) overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. Radiographic progression free survival (rPFS)

2.1 RECIST response to include:

- a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
- b. Disease control rate (DCR) as measured by RECIST v1.1 criteria

3.2 Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Alternate Primary endpoint

The primary endpoint is OS and is defined as the time from randomization to the date of death from any cause.

2.2.1.1 Key Secondary endpoints

The key secondary endpoints include the following:

Radiographic progression free survival (rPFS) rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha

Page 24 of 96

level; it is not required to statistically meet both rPFS and OS to be declared a positive study.
Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

Page 25 of 96

- c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
- 5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

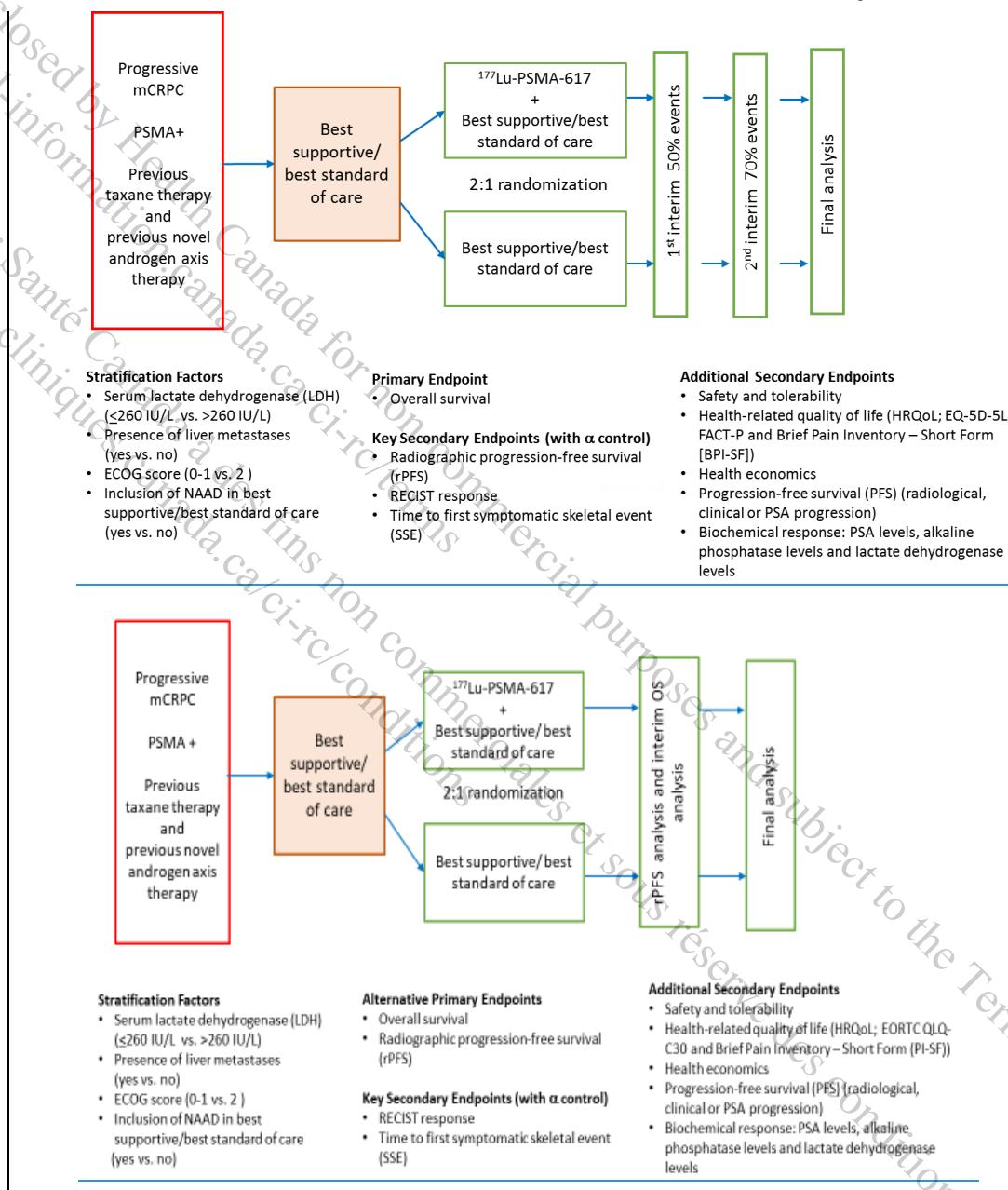


Figure 1 Diagram of trial design

Page 27 of 96

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ⁶⁸Ga-PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ¹⁷⁷Lu-PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ¹⁷⁷Lu-PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment,

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the treatment part of the study at any time. If a patient withdraws consent for the treatment part of the study, the patient will continue to be followed for long term follow up unless they specifically withdraw for the long term follow up of the study.

An End of Treatment (EOT) visit should occur once a patient is to enter discontinues the long term follow up treatment part of the study- for any reason (patient or investigator decision, going on to long term follow up, etc.).

Page 28 of 96

This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care, (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for up to 24 months or until 489 deaths have occurred. If a patient withdraws consent from the treatment part of the overall censoring rate for survival reduces to a level identified in the statistical analysis plan (SAP)-study, they will be asked to confirm if they will consent to all aspects of long term follow up, survival only or no long term follow up activity.

This study will enroll approximately 750 patients involving about 80110 sites worldwide.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternative endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (\pm 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Page 29 of 96

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ¹⁷⁷Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours ([Kratzschwil et al 2016](#)). [Kratzschwil et al 2016](#). PSMA-negative tissues like the bone marrow, are exposed transiently to ¹⁷⁷Lu-PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

¹⁷⁷Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious ([Hofman et al 2018](#)).

Clinical series now show reports of more than 4 cycles of ¹⁷⁷Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient ([Rahbar et al 2018](#)). [Rahbar et al 2018](#). In addition, a recent review suggests optimal dosing of 6 cycles of ¹⁷⁷Lu-PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq ([Emmett et al 2017](#)). [Emmett et al 2017](#). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ¹⁷⁷Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ¹⁷⁷Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ¹⁷⁷Lu-PSMA-617 administration in this clinical trial.

Page 30 of 96

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (≤ 260 IU/L vs. > 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient is to enter discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up part of the study, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or best supportive/best standard of care, (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period.

Total duration of the trial for randomized patients considering expected survival, is expected to be 19 to 23 months, including a 1-month screening period, 6 to 10-month treatment period and a long-term follow-up period for safety and survival lasting up to 24 months or at least until the overall censoring rate for survival reduces to a level identified in the SAP.

489 deaths have occurred. Total duration of the study, from first date of randomization to last follow-up, will be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue for approximately 38 months or until the overall censoring rate for survival reduces to a level identified in the SAP at least until 489 deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1 and Section 8.7.

For timing of the 2 formal interim analyses and any rules for early statistical curtailment, refer to Section 8.7 and Section 8.8.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. Participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

3. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga -PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have [prior orchiectomy and/or ongoing androgen deprivation therapy and](#) a castrate level of serum testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient is not willing to receive a second taxane regimen, or
 - b. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation or intolerance).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target

Page 32 of 96

lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.

- c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).

12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.

13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

- a. Bone marrow reserve:

- White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
- Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
- Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

- b. Hepatic:

- Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

- c. Renal:

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$

15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L)

16. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible.

[Inclusion #16 has been removed]

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

For patients who have partners of childbearing potential:

18. Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 36 months after last study drug administration.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 ~~or~~, hemi-body irradiation within 6 months prior to randomization. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion within 30 days of randomization. for the purpose of eligibility.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. Patients with adequately treated non-melanoma skin cancer, superficial bladder cancer and However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible. as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient only withdraws consent for the treatment part of the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety and survival follow-up unless he also specifically withdraws from the or survival only long-term follow-up period.

This trial design is intent to treat so that all subjects will be followed for approximately up to 24 months or until the overall censoring rate for safety and survival reduces to a level identified in the SAP or until 489 deaths have occurred. The total of 489 deaths are expected to have occurred approximately 15 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ⁶⁸Ga-PSMA-11

For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure. The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

5.1.15.1.2 Administration of ¹⁷⁷Lu-PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ¹⁷⁷Lu-PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ¹⁷⁷Lu-PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ¹⁷⁷Lu-PSMA-617 administration.

¹⁷⁷Lu-PSMA-617 will be administered slowly by the intravenous route through an indwelling catheter and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(\pm 5) minutes before and at 30(\pm 5) and 60(\pm 5) minutes following injectionadministration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ¹⁷⁷Lu-PSMA-617 administration should be recorded.

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 35 of 96

A decision to order ¹⁷⁷Lu-PSMA-617 should be communicated to the sponsor or designee no later than 4510 business days prior to the planned administration for each cycle.

5.1.25.1.3 Toxicity risk reduction and supportive care for ¹⁷⁷Lu-PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ¹⁷⁷Lu-PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ¹⁷⁷Lu-PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.35.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. [Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ¹⁷⁷Lu-PSMA-617](#). At the discretion of the investigator, a dose of ¹⁷⁷Lu-PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ¹⁷⁷Lu-PSMA-617 must be discontinued. Once a dose is reduced, treatment with ¹⁷⁷Lu-PSMA-617 should not be re-escalated.

If a treatment delay persists for >4 weeks, treatment with ¹⁷⁷Lu-PSMA-617 must be discontinued. If treatment with ¹⁷⁷Lu-PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: • Hemoglobin <10 g/dL • WBC count <3.0 × 10 ⁹ /L • ANC <1.5 × 10 ⁹ /L	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of < 75 × 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. <u>Reduce ¹⁷⁷Lu-PSMA-617 dose by 20% on the next cycle.</u> Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	<u>Hold ¹⁷⁷Lu-PSMA-617 administration until improvement to Grade 1 or baseline.</u> <u>Reduce ¹⁷⁷Lu-PSMA-617 dose by 20% on the next cycle</u>
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (<u>not amenable to medical intervention</u>)	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline <u>Reduce ¹⁷⁷Lu-PSMA-617 dose by 20% on the next cycle</u>
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

5.3.1.1 Concomitant medications/ supportive care

5.3.1.1.1 Permitted concomitant medications/ supportive care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm ~~will~~should be administered as per physician's orders and protocol at the institution, ~~and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization or shortly thereafter.~~ Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Page 38 of 96

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must remain castrate and receive a luteinizing hormone-releasing hormone analogue (agonist or antagonist) or polyestradiol phosphate throughout the study.

Other treatments for prostate cancer not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include: corticosteroids, antiandrogens, or ketoconazole.

Local external beam radiotherapy, including palliative external radiation is allowed.

Supportive care should be provided as deemed necessary by the treating physician.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section [5.1.35.1.4](#) for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
	<ul style="list-style-type: none">• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix H Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks (± 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

Protocol no. PSMA-617-01

Version no.: [42.0](#)

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

[22 March 2018](#) [16 January 2019](#)

Page 42 of 96

6.2.2 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.3 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.4 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.5 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)).[Rabin 2001](#) EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)).[EuroQoL Group 1990](#) This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)).[EuroQoL Group 2015](#) Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 43 of 96

different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)).[Cella et al 1993](#)) The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993](#)[Cella et al 1993](#), [Esper et al 1997](#))
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#)[Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.6 Health Economics

A health economics (HE) sub-study will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.7 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.8 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry

sodium

Sodium

- potassium
- total and direct bilirubin
- ALP
- AST
- ALT

Urinalysis

urine pH

- protein content
- specific gravity
- appearance and color

Hematology

complete blood count (white blood cell count and differential)

- red blood cell count
- hemoglobin
- hematocrit
- platelet count

LDH

blood urea nitrogen

creatinine

uric acid

phosphorus

chloride

bicarbonate*

calcium

glucose

total protein

albumin

*total carbon dioxide or equivalent is acceptable

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (eg, condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 6 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect [self-reported, long term follow up specific AE](#) assessments, and survival and treatment updates from patients every 3 months (± 1 month) via phone, email, or letter. Hematology and chemistry blood work will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study will be asked for permission to continue long-term status updates.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Progression of disease is not considered an AE or SAE for this study.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death; except for deaths due to progression of disease• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All adverse events (AEs) will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the last dose or intervention identified as best supportive/best standard of care, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

AE monitoring for treatment emergent ⁶⁸Ga-PSMA-11 events will begin with the administration of ⁶⁸Ga-PSMA-11 and continue for a period of at least 6 days and will continue up to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and up to Cycle 1 Day 1 for the best supportive/best standard of care only arm. AE monitoring for treatment emergent ¹⁷⁷Lu-PSMA-617 events will commence with initial dosing of ¹⁷⁷Lu-PSMA-617 and continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617. AE monitoring for the best supportive/best standard of care only arm will commence with Cycle 1 Day 1 and continue up to and including 30 days after the last dose of best supportive/best standard of care.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or ¹⁷⁷Lu-PSMA-617 best supportive/best standard of care, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email

Page 47 of 96

indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ⁶⁸Ga-PSMA-11 and/or, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

All statistical analyses will be carried out using SAS version 9.3 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 48 of 96

of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Sample size and power determination

The sample size was determined based on the alternate primary endpoint:endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 750 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 13 months and a follow-up of 24 months (or until the the overall censoring rate for survival reduces to a level identified in the SAP), a total of 750 patients randomized will yield 489 eventsis expected to yield (i) 457 rPFS events and 249 deaths with a minimum follow-up of 3.4 months after the last patient is randomized and (ii) 489 death events with a minimum follow-up of 15 months after the last patient is randomized. Central independent assessments will be used to determine rPFS events.

With two interim The analyses of rPFS and OS are event driven. The analysis of rPFS is planned with 457 events with an allocated 1-sided alpha level of 0.001. An interim analysis of OS is planned to coincide with this analysis of rPFS at 50% (243/489, which time 249 deaths are expected approximately 16.5 ; the allocated 1-sided alpha level for OS at the interim will be 0.001. A final analysis of OS will take place with 489 deaths which are expected to have accrued with 15 months after first follow-up post the last patient randomized) and 70% (344/489, expected approximately 20.5 months after first patient randomized) events with adjusted 1-sided p values of 0.00153 and 0.00690 respectively and a 1-sided p value. The alpha level applicable to OS in the final analysis of will depend upon the earlier rPFS and interim OS results:

- if both achieve $p < 0.02266$, this trial has 0.001 1-sided, then the alpha level for the final analysis of OS will be 0.025 1-sided.
- if only one reaches $p < 0.001$ 1-sided, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if neither reaches $p < 0.001$ 1-sided, then the alpha level for the final analysis of OS will be 0.023 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; overall power is at least 91.4% and the overall Type I error rate of is ≤ 0.025 1-sided.

The observed HRs that will meet the stated p value thresholds at the first $p < 0.001$ for rPFS and second the interim analyses, and at the final analysis of OS are 0.669, 0.754736 and 0.825,660 respectively (corresponding to the observed HR that will meet $p < 0.023$ to 4.9 month, 3.3 month, and 2.1 month increases $p < 0.025$ in median overall survival assuming median OS on best supportive/best standard of care the final analysis of 10 months). The cumulative probabilities of

Page 49 of 96

stopping at the first and second interims under the alternative hypothesis OS are 35.4% and 61.3% respectively 0.826 to 0.829.

8.2 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. Patient efficacy data in this dataset will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.3 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.4 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.5 Efficacy analyses

8.5.1 PrimaryAlternate primary endpoint efficacy analysis

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause.

8.5.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 50 of 96

Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. The analysis of rPFS is event driven and will take place once 457 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.001 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up or are alive at the time of analysis will be censored for rPFS at the time they were of their last known to be alive radiographic assessment or at the data cut-off date of event cut off for OS analysis. OS. rPFS data will be displayed using Kaplan Meier curves from which median OSrPFS times will be estimated for both treatment arms.

A stratified Cox proportional hazards regression model will be used to analyze OSrPFS in the FAS dataset. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors. The HR (active: control), its 95% confidence interval, and the associated 2-sided p-value will be presented. A supportive analysis will be provided via a stratified log-rank test, stratifying again for the randomization stratification factors.

8.5.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 457 rPFS events); it is anticipated that approximately 249 deaths will have accrued at the time of the rPFS analysis. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 489 deaths have occurred. As described in Section 8.1, the allocated alpha level for the final OS analysis will be between 0.023 and 0.0251-sided, depending on the results of the earlier rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed in the same manner as rPFS.

8.5.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level or OS to meet its allocated alpha level at either (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) or (ii) at the final OS analysis with 489 deaths.

Alpha allocation and recycling is used to ensure control of the overall Type I error rate as described in Section 8.1.

Page 51 of 96

8.5.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

~~12+PFS~~

1. RECIST ORR and DCR
2. Time to SSE

Time to SSE ~~and PFS~~ will be analyzed using a Cox regression model in the same manner as described for the alternate primary endpointendpoints. Objective response and disease control rate will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response ~~endpoint~~ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if ~~the~~either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure-at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the ~~3~~two key secondary endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints are:

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints (e.g. PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for the alternate primary endpointendpoints

Page 52 of 96

except using a 2-sided p-value. Disease control rate DCR will be analyzed in the same manner as objective response rate and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#)[Ellis et al 2008](#).

8.6 Safety analyses

8.6.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.6.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ⁶⁸Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ⁶⁸Ga-PSMA-11 but appeared following dosing, or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of the first dose of ⁶⁸Ga-PSMA-11 dosing up to 6 days after the date of the initial dose of ⁶⁸Ga-PSMA-11 or dosing as long as prior to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ⁶⁸Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ⁶⁸Ga-PSMA-11 TEAEs. Unrelated ⁶⁸Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A ¹⁷⁷Lu PSMA 617 randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment with, defined as first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the date of the first dose of ¹⁷⁷Lu PSMA-617 initiation of randomized treatment up to 30 days after the date of the last dose of ¹⁷⁷Lu-PSMA-617 or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.6.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.6.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.7 IDMC and Interim analysesData Evaluation

8.7.1 Interim efficacy analyses

As described above in Section 8.1, two formal interim efficacy analyses are planned at 50% and 70% of the total planned number of events. The purpose of these interim analyses is to allow early stopping for efficacy should sufficient statistical evidence be found to reject the null hypothesis of no survival effect. There IDMC

An IDMC will be no assessment for futility.

These interim analyses will be overseen by a fully Independent Data Monitoring Committee (IDMC) who may recommend stopping convened to review accumulating safety and safeguard patient interest in the study for superior efficacy at the first or second interim if the corresponding pre-specified 1-sided p-value threshold is met. An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any interim analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision to continue or stop the trial based on either interim analysis.

8.7.2 Interim safety analyses

Safety data monitoring interim analyses will be conducted quarterly by the IDMC. These analysessafety reviews will commence following the completion of the first three months of study accrual.

8.8 Criteria for termination of trial

Safety data will be reviewedIn addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS at 457 events, interim OS at the time of the rPFS analysis and final OS with 489 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on an ongoing the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC who will provide recommendations as necessary members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding the ongoing conduct of the study. The trial may also be terminated due to an early whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy completion.

Page 54 of 96

8.7.2 Formal Interim Analysis of study enrollment and treatment/OS

As described above in Section 8.1, one formal interim analysis is planned for OS to take place at the time of the rPFS analysis. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 489 OS events have accrued at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 55 of 96

case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative [and by the person who obtained the authorization](#).

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

22 March 2018 16 January 2019

Page 56 of 96

review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

Page 57 of 96

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

Protocol no. PSMA-617-01

Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 58 of 96

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

Disclosed to Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

14. REFERENCES

Ahmadzadehfar et al 2016

Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmadzadehfar et al 2015

Ahmadzadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015, 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Page 60 of 96

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI/UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Page 61 of 96

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. [68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0](#). Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ¹⁷⁷Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [¹⁷⁷Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Hofman et al 20172018

Hofman MS, Sandhu S, Eu P, PriceViolet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, et al. [Lutetium-177 Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. \[¹⁷⁷Lu\]-PSMA \(¹⁷⁷LuPSMA\) theranostics phase II trial: Efficacy, safety, and QoL](#) [617 radionuclide treatment](#) in patients with [eastrate](#)[metastatic castration](#)-resistant prostate cancer [treated with LuPSMA. \[abstract/presentation\]](#) In 2017 European Society for Medical Oncology Annual Meeting; 2017 Sep 8-12; Madrid, Spain. Ann(LuPSMA trial): a

Page 62 of 96

[single-centre, single-arm, phase 2 study. Lancet Oncol 2017; 28 \(suppl_5\):v269 -v294. 2018 Jun;19\(6\):825-833.](#)

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987-88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanová M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of Oncology 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With ¹⁷⁷Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. Clin Nucl Med. 2016a;41(7):522-528.

Page 63 of 96

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of ^{177}Lu -PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating ^{177}Lu -PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res.* 2003;9:6357-62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. *J Natl Cancer Inst.* 2004;96(11):879-82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. *PLoS One.* 2015 Oct 13;10(10):e0139440.

Page 64 of 96

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. *J Clin Oncol* 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. *Cancer Statistics*, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes.* 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S213 EPW14.

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. *Ann Oncol.* 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ¹⁷⁷Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2017;44(1):81-91.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesely S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. *Can Urol Assoc J.* 2014 Jul;8(7-8):E520-3.

Page 65 of 96

Appendix 1 Schedules of Assessments

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X			XX		X
AE monitoring ^a	X			XX		X
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit.					

^a Adverse event monitoring for treatment-emergent ^{177}Lu -PSMA-617 events will commence with initial dosing at time of ^{177}Lu -PSMA-617 consent.

^b Within Can be done up to 3 days prior to Day 1. For hematology and chemistry: within up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within up to 3 days of Day 1) and at 15(\pm 5) minutes before, 30 (\pm 5) minutes post, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no. 42.0

Endocyte, Inc.
22 March 2018/16 January 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6*	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 8 weeks (± 1 week)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X					X ^a	X ^a	X	
AE monitoring ^b	X					X ^a	X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}					X ^{e,h}		X ^h	
FACT-P	X ^{e,h}					X ^{e,h}		X ^h	
BPI-SF	X ^{e,h}					X ^{e,h}		X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	
Serum testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days) through the end of treatment visit								

* After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and

Protocol no. PSMA-617-01
Version no. 42.0

Endocyte, Inc.
22 March 2018/16 January 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

- ^a Phone evaluation evaluations are allowed during Weeks 2, 4, and 6, but are not required for visits after Day 1 of each cycle.
- ^b Adverse event monitoring for treatment-emergent ¹⁷⁷Lu-PSMA-617 events will commence with initial dosing of ¹⁷⁷Lu-PSMA-617 and continue at time of consent.
- ^c Can be done up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617.
- ^d Within 3 days prior to Day 1. For hematology and chemistry: within up to 3 days prior to Days 1, 15, and 28.
- ^e Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within up to 3 days of Day 1) and at 15(^{+/−5}) minutes before, 30(^{+/−5}) minutes post, and 60(^{+/−5}) minutes post ¹⁷⁷Lu-PSMA-617 administration.
- ^f To be completed prior to drug administration (if applicable) on Day 1.
- ^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (± 1 week). If at any time, WBC count $<3.0 \times 10^9/L$, ANC is $<1.5 \times 10^9/L$, platelet count is $<100 \times 10^9/L$ or hemoglobin level is $<9\text{ g/dL}$, hematologic parameters (i.e., CBC with differential analysis) should be done no less frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a \geq Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.
- ^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study
- ^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X			XX		X
AE monitoring ^b	X			XX		X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care Cycle 1 Day 1 ^g for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Within up to 3 days prior to Day 1. For hematology and chemistry: within up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will begin Cycle 1 Day 1 commence at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no. 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018/16 January 2019

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6						After Cycle 6	End of Treatment ^f	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 8 weeks (\pm 1 week)		Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X-----					X ^a	X ^a	X	
AE monitoring	X-----					X ^a	X ^a	X	
Weight	X ^b						X ^b	X	
ECOG	X ^b						X ^b	X	
Directed physical exam	X ^b						X ^b	X	
Vital signs ^c	X ^b						X ^b	X	
EQ-5D-5L	X ^{d,g}						X ^{d,g}	X ^{d,g}	
FACT-P	X ^{d,g}						X ^{d,g}	X ^{d,g}	
BPI-SF	X ^{d,g}						X ^{d,g}	X	
Best supportive/best standard of care	As per physician's orders						As per physician's orders		
Hematology ^e	X ^b		X ^b		X ^b		X ^b	X	
Chemistry ^e	X ^b		X ^b		X ^b		X ^b	X	
Serum testosterone	X ^b						X ^b	X	
PSA	X ^b						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of careCycle 1 Day 1 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the end of treatment visit								

^a Phone evaluations are allowed during Weeks 2, 4, and 6, but are not required for visits after Day 1 of each cycle.

^b Within 3 days prior to Day 1. For hematology and chemistry: within up to 3 days prior to Days 1, 15, and 29.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within up to 3 days of Day 1).

^d To be completed prior to drug administration (if applicable) on Day 1.

^e For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 weeks (\pm 1 week). If at any time, WBC < 3.0 \times 10⁹/L, ANC is < 1.5 \times 10⁹/L, platelet count is < 100 \times 10⁹/L or hemoglobin level is < 9 g/dL, hematologic parameters (i.e., CBC with differential analysis) should be done no less

Protocol no. PSMA-617-01

Version no. 42.0

Endocyte, Inc.

22 March 2018/16 January 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 71 of 96

frequently than once each week until resolution to Grade 1 or baseline. If at any time there is a Grade 2 related chemistry lab result, chemistry should be done no less frequently than once each week until resolution to Grade 1 or baseline.

f To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose or intervention of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

g HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Page 72 of 96

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Page 73 of 96

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Page 74 of 96

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Page 75 of 96

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 76 of 96

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Page 77 of 96

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 | 16 January 2019

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Page 79 of 96

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Record outcome as new lesions, no new lesions or resolved lesion• First scheduled reassessment:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ New lesions: perform a confirmatory scan 6 or more weeks later• Confirmatory scan:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ Additional new lesions: progression• Subsequent scheduled reassessments:<ul style="list-style-type: none">◦ No new lesions: continue◦ New lesions: progression• Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">• Exclude pseudoprogression in the absence of symptoms or other signs of progression• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented• For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan• Date of progression is the date of the scan that first documents the second lesion• Changes in intensity of uptake alone do not constitute either progression or regression• Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, \geq 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve end points:</p> <ul style="list-style-type: none">• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 80 of 96

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 81 of 96

Brief Pain Inventory (Short Form)

Time: ____ : ____ AM PM
Today's Date (day, month, year):

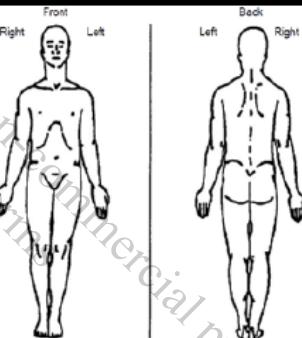
Today's Date (day, month, year).
JAN JAN MAR MAR MAY MAY JUL JUL SEP SEP NOV NOV
FEB FEB APR APR JUN JUN AUG AUG OCT OCT DEC DEC

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.



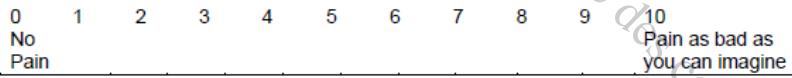
4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.



5. Please rate your pain by circling the one number that best describes your pain on the average.



6. Please rate your pain by circling the one number that best describes how much pain you have right now.



Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of

Protocol no. PSMA-617-01
Version no.: 12.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 82 of 96

Today's Date (Day, Month, Year): _____ (Example: 08-FEB-2016) DAY MONTH YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 83 of 96

**Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5
Level scale) (sample only, not for patient use)**

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 84 of 96



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

Page 85 of 96

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

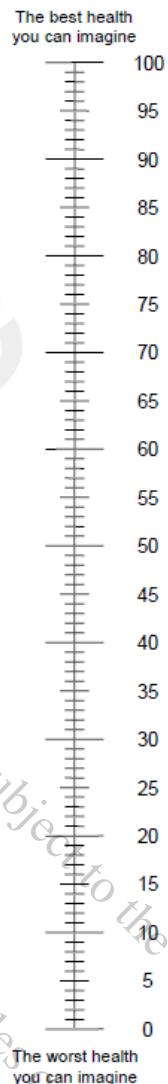
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 86 of 96

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 87 of 96

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy -
Prostate) (sample only, not for patient use)**

| Protocol no. PSMA-617-01
Version no.: 42.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 March 2018 16 January 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Somewhat	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 91 of 96

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 12.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

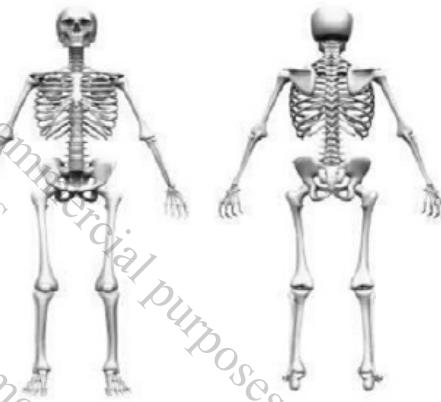
Endocyte, Inc.
22 March 2018 16 January 2019

Page 92 of 96

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 8 BASELINE Scan

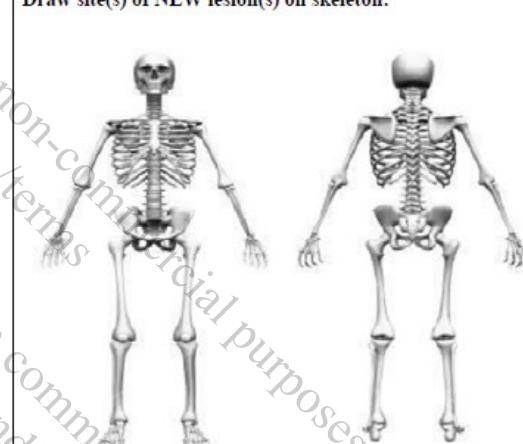
Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input checked="" type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
* Presence of new lesions at this time does not confirm progression	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed): 	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

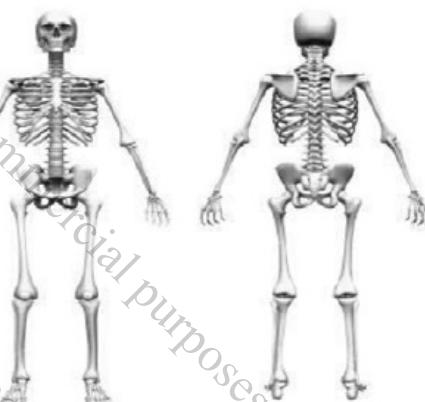
Page 95 of 96

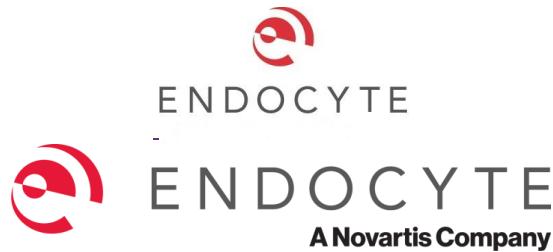
Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date:	<p>DD-MM-YY</p>
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 96 of 96

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date:	<p>DD-MM-YY</p>
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 23.0

Date: 16 January 2019

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)
133,925 or site equivalent (⁶⁸Ga-PSMA-11)

EudraCT No. 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617; ⁶⁸Ga-PSMA-11

Sponsor: Endocyte, Inc., A Novartis Company
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer:

Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Page 2 of 112

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

| Protocol No./Acronym: *from Title page*
Version No.: *from Title page*

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
20 December 2018 / 01 April 2019

Page 3 of 112

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Protocol no. PSMA-617-01
Version no.: 24.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Table of Contents

Site Principal Investigator Signature	3
Table of Contents	4
Revision History	12
Clinical Trial Summary	13
List of Abbreviations and Definitions	15
1. Introduction	17
1.1 Background information	17
1.2 Summary of nonclinical studies with clinical significance	21
1.3 Summary of known and potential risks and benefits	22
2. Trial Objectives and Endpoints	23
2.1 Trial objectives	23
2.1.1 Primary objective	23
2.1.2 Key secondary objectives	23
2.1.3 Additional secondary objectives	23
2.2 Trial endpoints	23
2.2.1 Alternate Primary endpoints	23
2.2.2 Key Secondary endpoints	24
2.2.3 Additional Secondary endpoints	24
3. Trial Design	25
3.1 Overview of the clinical trial design	25
3.2 Rationale for the study design	28
3.3 Measures taken to minimize/avoid bias	28
3.4 Description of the clinical trial	29
3.4.1 Description of investigational medicinal product	29
3.4.2 Dosage and rationale for dose selection	29
3.4.3 Subject allocation to treatment	30
3.4.4 End of treatment visit	30
3.4.5 Duration of Subject Participation	30
3.5 End of trial definition	31
4. Selection and Withdrawal of Subjects	31
4.1 Inclusion criteria	31
4.2 Exclusion criteria	33
4.3 Subject withdrawal of consent for study or treatment	34
5. Treatment of Subjects	34
5.1 Treatment with the investigational medicinal product	34

Page 5 of 112

5.1.1	Administration of ⁶⁸ Ga PSMA-11	34
5.1.2	Administration of ¹⁷⁷ Lu PSMA-617	34
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu PSMA-617 injections	35
5.1.4	Management of toxicity adverse events: dosing delays and modification	35
5.2	Best supportive/best standard of care	37
5.3	Concomitant medications/ supportive care	38
5.3.1	Permitted concomitant medications/ supportive care	38
5.3.2	Prohibited concomitant medications	38
5.4	Monitoring treatment compliance	39
5.5	Treatment discontinuation	39
6.	Study Assessments and Procedures	39
6.1	Screening procedures and baseline assessments	39
6.2	Efficacy assessments	41
6.2.1	Radiographic imaging for tumor assessments	41
6.2.2	RECIST criteria	42
6.2.3	Symptomatic skeletal events	42
6.2.4	Pain score	42
6.2.5	Health related quality of life	42
6.2.6	Health Economics	43
6.2.7	Clinical progression	43
6.2.8	PSA levels	44
6.3	Safety assessments	44
6.3.1	Clinical laboratory evaluations	44
6.3.2	Vital signs	45
6.3.3	Electrocardiograms	45
6.3.4	Birth Control	45
6.4	End of treatment visit procedures	45
6.5	Long term follow up procedures	45
7.	Adverse Events	46
7.1	Adverse event definitions	46
7.2	Evaluating and recording adverse events	47
7.3	Immediate Adverse Event Reporting	47
7.3.1	Serious Adverse Events	47
7.3.2	Serious adverse event subject follow up	48
7.3.3	Sponsor Contact Information for Immediate Reporting	48
8.	Statistics	48

Page 6 of 112

8.1	Sample size and power determination	49
8.2	Analysis populations	49
8.3	Demographics and baseline disease characteristics	50
8.4	Patient disposition	50
8.5	Efficacy analyses	50
8.5.1	Alternate primary endpoint efficacy analysis	50
8.5.2	Secondary efficacy analyses	51
8.6	Safety analyses	52
8.6.1	Extent of exposure	52
8.6.2	Analysis of adverse events	53
8.6.3	Analysis of laboratory assessments	53
8.6.4	Analysis of vital sign data	53
8.7	IDMC and Interim Data Evaluation	53
8.7.1	IDMC	53
8.7.2	Formal Interim Analysis of OS	54
9.	Access to Source Data/Documents	54
10.	Ethics	54
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	54
10.2	Informed consent	55
10.3	Health Insurance Portability and Accountability Act	55
10.4	Confidentiality	55
11.	Compliance and quality control	56
11.1	Compliance with Monitoring and Audits	56
12.	Data Handling, Record Keeping, and Compliance	56
12.1	Investigational medicinal product accountability	56
12.2	Breaking the blind	56
12.3	Data collection forms and source document identification	57
12.4	Record maintenance and retention	57
12.5	Archiving	58
13.	Publication Policy	58
14.	References	59
Appendix 1	Schedules of Assessments	66
Appendix 2	Suggested treatment guidelines	87
Appendix 3	Principal Investigator Signature	88
Appendix 4a	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	89

Page 7 of 112

<u>Appendix 4b</u> Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	90
<u>Appendix 5</u> Common Terminology Criteria for Adverse Events	91
<u>Appendix 6</u> Response Evaluation Criteria in Solid Tumors	92
<u>Appendix 7</u> Prostate Cancer Working Group 3 Recommendations	93
<u>Appendix 8</u> BPI SF (<i>sample only, not for patient use</i>)	95
<u>Appendix 9</u> EQ 5D-5L (European Quality of Life (EuroQol) -5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	98
<u>Appendix 10</u> FACT P (Functional Assessment of Cancer Therapy -Prostate) (<i>sample only, not for patient use</i>)	102
<u>Appendix 11</u> PCCTC Bone Scan Assessment Tool	106
<u>Site Principal Investigator Signature</u>	3
<u>Table of Contents</u>	4
<u>Revision History</u>	12
<u>Clinical Trial Summary</u>	13
<u>List of Abbreviations and Definitions</u>	15
<u>1.</u> <u>Introduction</u>	17
<u>1.1</u> <u>Background information</u>	17
<u>1.2</u> <u>Summary of nonclinical studies with clinical significance</u>	21
<u>1.3</u> <u>Summary of known and potential risks and benefits</u>	22
<u>2.</u> <u>Trial Objectives and Endpoints</u>	23
<u>2.1</u> <u>Trial objectives</u>	23
<u>2.1.1</u> <u>Primary objective</u>	23
<u>2.1.2</u> <u>Key secondary objectives</u>	23
<u>2.1.3</u> <u>Additional secondary objectives</u>	23
<u>2.2</u> <u>Trial endpoints</u>	23
<u>2.2.1</u> <u>Alternate Primary endpoints</u>	23
<u>2.2.2</u> <u>Key Secondary endpoints</u>	24
<u>2.2.3</u> <u>Additional Secondary endpoints</u>	24
<u>3.</u> <u>Trial Design</u>	25
<u>3.1</u> <u>Overview of the clinical trial design</u>	25
<u>3.2</u> <u>Rationale for the study design</u>	28
<u>3.3</u> <u>Measures taken to minimize/avoid bias</u>	28
<u>3.4</u> <u>Description of the clinical trial</u>	29
<u>3.4.1</u> <u>Description of investigational medicinal product</u>	29
<u>3.4.2</u> <u>Dosage and rationale for dose selection</u>	29
<u>3.4.3</u> <u>Subject allocation to treatment</u>	30

Page 8 of 112

3.4.4	End of treatment visit	30
3.4.5	Duration of Subject Participation	30
3.5	End of trial definition.....	31
4.	Selection and Withdrawal of Subjects	31
4.1	Inclusion criteria	31
4.2	Exclusion criteria	33
4.3	Subject withdrawal of consent for study or treatment	34
5.	Treatment of Subjects	34
5.1	Treatment with the investigational medicinal product.....	34
5.1.1	Administration of ⁶⁸ Ga-PSMA-11.....	34
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-617	34
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	35
5.1.4	Management of toxicity adverse events: dosing delays and modification	35
5.2	Best supportive/best standard of care	37
5.3	Concomitant medications/ supportive care	38
5.3.1	Permitted concomitant medications/ supportive care	38
5.3.2	Prohibited concomitant medications	38
5.4	Monitoring treatment compliance	39
5.5	Treatment discontinuation	39
6.	Study Assessments and Procedures	39
6.1	Screening procedures and baseline assessments	39
6.2	Efficacy assessments.....	41
6.2.1	Radiographic imaging for tumor assessments.....	41
6.2.2	RECIST criteria.....	42
6.2.3	Symptomatic skeletal events	42
6.2.4	Pain score	42
6.2.5	Health-related quality of life	42
6.2.6	Health Economics	43
6.2.7	Clinical progression.....	43
6.2.8	PSA levels	44
6.3	Safety assessments	44
6.3.1	Clinical laboratory evaluations.....	44
6.3.2	Vital signs.....	45
6.3.3	Electrocardiograms.....	45
6.3.4	Birth Control	45
6.4	End of treatment visit procedures	45
6.5	Long-term follow-up procedures	45

Protocol no. PSMA-617-01

Version no.: 22.0

April 2019

Endocyte, Inc.

16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 9 of 112

<u>7.</u>	<u>Adverse Events</u>	<u>46</u>
<u> 7.1</u>	<u> Adverse event definitions</u>	<u>46</u>
<u> 7.2</u>	<u> Evaluating and recording adverse events.....</u>	<u>47</u>
<u> 7.3</u>	<u> Immediate Adverse Event Reporting.....</u>	<u>47</u>
<u> 7.3.1</u>	<u> Serious Adverse Events.....</u>	<u>47</u>
<u> 7.3.2</u>	<u> Serious adverse event subject follow-up.....</u>	<u>48</u>
<u> 7.3.3</u>	<u> Sponsor Contact Information for Immediate Reporting.....</u>	<u>48</u>
<u>8.</u>	<u>Statistics</u>	<u>48</u>
<u> 8.1</u>	<u> Sample size and power determination</u>	<u>49</u>
<u> 8.2</u>	<u> Analysis populations.....</u>	<u>49</u>
<u> 8.3</u>	<u> Demographics and baseline disease characteristics.....</u>	<u>50</u>
<u> 8.4</u>	<u> Patient disposition.....</u>	<u>50</u>
<u> 8.5</u>	<u> Efficacy analyses</u>	<u>50</u>
<u> 8.5.1</u>	<u> Alternate primary endpoint efficacy analysis</u>	<u>50</u>
<u> 8.5.2</u>	<u> Secondary efficacy analyses.....</u>	<u>51</u>
<u> 8.6</u>	<u> Safety analyses.....</u>	<u>52</u>
<u> 8.6.1</u>	<u> Extent of exposure.....</u>	<u>52</u>
<u> 8.6.2</u>	<u> Analysis of adverse events</u>	<u>53</u>
<u> 8.6.3</u>	<u> Analysis of laboratory assessments.....</u>	<u>53</u>
<u> 8.6.4</u>	<u> Analysis of vital sign data</u>	<u>53</u>
<u> 8.7</u>	<u> IDMC and Interim Data Evaluation.....</u>	<u>53</u>
<u> 8.7.1</u>	<u> IDMC</u>	<u>53</u>
<u> 8.7.2</u>	<u> Formal Interim Analysis of OS</u>	<u>54</u>
<u>9.</u>	<u>Access to Source Data/Documents</u>	<u>54</u>
<u>10.</u>	<u>Ethics.....</u>	<u>54</u>
<u> 10.1</u>	<u>Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)</u>	<u>54</u>
<u> 10.2</u>	<u>Informed consent.....</u>	<u>55</u>
<u> 10.3</u>	<u>Health Insurance Portability and Accountability Act.....</u>	<u>55</u>
<u> 10.4</u>	<u>Confidentiality.....</u>	<u>55</u>
<u>11.</u>	<u>Compliance and quality control</u>	<u>56</u>
<u> 11.1</u>	<u>Compliance with Monitoring and Audits</u>	<u>56</u>
<u>12.</u>	<u>Data Handling, Record Keeping, and Compliance</u>	<u>56</u>
<u> 12.1</u>	<u>Investigational medicinal product accountability.....</u>	<u>56</u>
<u> 12.2</u>	<u>Breaking the blind</u>	<u>56</u>
<u> 12.3</u>	<u>Data collection forms and source document identification</u>	<u>57</u>
<u> 12.4</u>	<u>Record maintenance and retention</u>	<u>57</u>

Page 10 of 112

<u>12.5 Archiving</u>	<u>58</u>
<u>13. Publication Policy.....</u>	<u>58</u>
<u>14. References</u>	<u>59</u>
<u>Appendix 1 Schedules of Assessments</u>	<u>66</u>
<u>Appendix 2 Suggested treatment guidelines</u>	<u>87</u>
<u>Appendix 3 Principal Investigator Signature</u>	<u>88</u>
<u>Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	<u>89</u>
<u>Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	<u>90</u>
<u>Appendix 5 Common Terminology Criteria for Adverse Events</u>	<u>91</u>
<u>Appendix 6 Response Evaluation Criteria in Solid Tumors</u>	<u>92</u>
<u>Appendix 7 Prostate Cancer Working Group 3 Recommendations.....</u>	<u>93</u>
<u>Appendix 8 BPI-SF (<i>sample only, not for patient use</i>).....</u>	<u>95</u>
<u>Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)</u>	<u>98</u>
<u>Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (<i>sample only, not for patient use</i>)</u>	<u>102</u>
<u>Appendix 11 PCCTC Bone Scan Assessment Tool</u>	<u>106</u>

List of tables

<u>Table 1 Toxicity management and dose modification recommendations</u>	<u>29</u>
<u>Table 2 Screening procedures and baseline assessments</u>	<u>32</u>
<u>Table 3 Schedule of assessments: ^{177}Lu PSMA 617 plus best supportive/best standard of care arm (Cycle 1)</u>	<u>57</u>
<u>Table 4 Schedule of assessments: ^{177}Lu PSMA 617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)</u>	<u>58</u>
<u>Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	<u>60</u>
<u>Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	<u>61</u>
<u>Table 1 Toxicity management and dose modification recommendations</u>	<u>36</u>
<u>Table 2 Screening procedures and baseline assessments</u>	<u>39</u>

Page 11 of 112

<u>Table 3</u>	<u>Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)</u>	<u>67</u>
<u>Table 4</u>	<u>Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....</u>	<u>68</u>
<u>Table 5</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	<u>78</u>
<u>Table 6</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	<u>79</u>

List of figures

<u>Figure 1</u>	<u>Diagram of trial design.....</u>	<u>26</u>
<u>Figure 1</u>	<u>Diagram of trial design.....</u>	<u>26</u>

Protocol no. PSMA-617-01
Version no.: 2.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 12 of 112

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment: AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment: AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	<u>01 April 2019</u>	<ul style="list-style-type: none">● Updated sponsor name.● Updated background information data.● Clarified rPFS is an alternate primary endpoint.● Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.● After Cycle 6, visits are now every 12 weeks (+/- 4 days)● Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.● Plasma testosterone was added as an acceptable form of testosterone testing.● Window for QOL and Pain questionnaires added.● Updated reference section

Protocol no. PSMA-617-01
Version no.: 2.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 13 of 112

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare the two alternative<ins>alternate</ins> primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory - Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>A long-term follow-up period will include the collection of survival and treatment updates<ins>information about new treatments, along with the patient's response to these treatments</ins>, adverse events assessment, as well as blood and for<ins>and</ins> hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (\pm1 month) via phone, email, or letter for up to 24 months or until 489 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).</p> <p>These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be</p>

Protocol no. PSMA-617-01
Version no.: ~~20.0~~
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 14 of 112

	<p>able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or best supportive/best standard of care (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 750 patients.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum/plasma testosterone and PSA levels will be measured up to 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (up to 3 days prior to each time point) and up to 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every <u>812</u> weeks (± 1 week 4 days) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	There will be 1 analysis at the time of 457 rPFS events where rPFS and OS will be evaluated for efficacy, followed by a final analysis of OS when 489 OS events have occurred. This trial has at least 91.5% overall power and an overall Type I error rate of at most 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

Page 15 of 112

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory - Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) - 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous

Page 16 of 112

Abbreviation	Term/Definition
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

| Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

| This information is confidential or privileged information and trade secrets of Endocyte, Inc.

| Endocyte, Inc.
16 January01

Page 17 of 112

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Hofman et al 2019)

[Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Clin Oncol. 2019;37\(suppl 7S\): 228.](#)

Page 18 of 112

Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life (Cella et al 2009). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal (Zielinski et al 2014).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 34% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months (Azad et al 2015, Cheng et al 2015, Badrising et al 2014, Brasso et al 2015, Loriot et al 2013, Noonan et al 2013). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998,

Page 19 of 112

Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ¹⁷⁷Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

¹⁷⁷Lu-PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ¹⁷⁷Lu-PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ¹⁷⁷Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (⁶⁸Ga), lutetium-177 (¹⁷⁷Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (⁹⁰Y).

¹⁷⁷Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ¹⁷⁷Lu is a medium- β -energy β -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ¹⁷⁷Lu provides better irradiation of small tumors, in contrast to the longer β -range of ⁹⁰Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ¹⁷⁷Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ¹⁷⁷Lu-PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ¹⁷⁷Lu to prostate cancer cells.

¹⁷⁷Lu-PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ¹⁷⁷Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kulkarni et al 2018)

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA

Page 20 of 112

[ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research.](#)
[2018 Jul;78\(13\):CT015.](#)

Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ¹⁷⁷Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ¹⁷⁷Lu-PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ¹⁷⁷Lu-PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in [compassionate use studies](#) the prospective study xerostomia appears low grade and occurs at a rate of approximately 887% in treated patients. Clearance of ¹⁷⁷Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 7067% respectively.

The first published clinical series of ¹⁷⁷Lu-PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ¹⁷⁷Lu-PSMA-617 in 3050 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018](#)), [Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 5764% of patients on ¹⁷⁷Lu-PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 4344% had a reduction of PSA of 80% or more. In 1727 patients with measurable disease, the objective response rate in measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 8256% (complete response [CR] and partial response [PR]). Median overall survival

Page 21 of 112

was 13.53 months—(95% confidence interval [CI] 10.5-18.0). Therapy with ¹⁷⁷Lu-PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 2040 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ¹⁷⁷Lu-PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ¹⁷⁷Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series have confirmed 8% indicate the most common side effects, predominately Grade 1-2, of ¹⁷⁷Lu-PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to xerostomia, less than 10% asymptomatic reversible hematological of Grade 3 to 4 toxicity and no significant renal toxicity events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

***In vitro* PSMA affinity and internalization studies**

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 22 of 112

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27-fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Fendler et al 2017).

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly, and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70-67% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2018 - Hofman et al 2019). In the trial, 3050 mCRPC patients were dosed with up to 4 cycles of 4-8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 23 of 112

most common treatment related AE was Grade 1 dry mouth, recorded in 87% of patients. The incidence of drug related Grade 3 or 4 neutropenia, anemia and thrombocytopenia were 7%, 13% and 13% respectively. The only other Grade 3 or 4 drug related toxicity were Grade 3 lymphocytopenia and pain in 37% and 3%, respectively, of patients. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternative/alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive 177Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics

Page 24 of 112

4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Alternate Primary endpoints

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

| rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics

| Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

| This information is confidential or privileged information and trade secrets of Endocyte, Inc.

| Endocyte, Inc.
16 January01

Page 25 of 112

4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
 - c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in

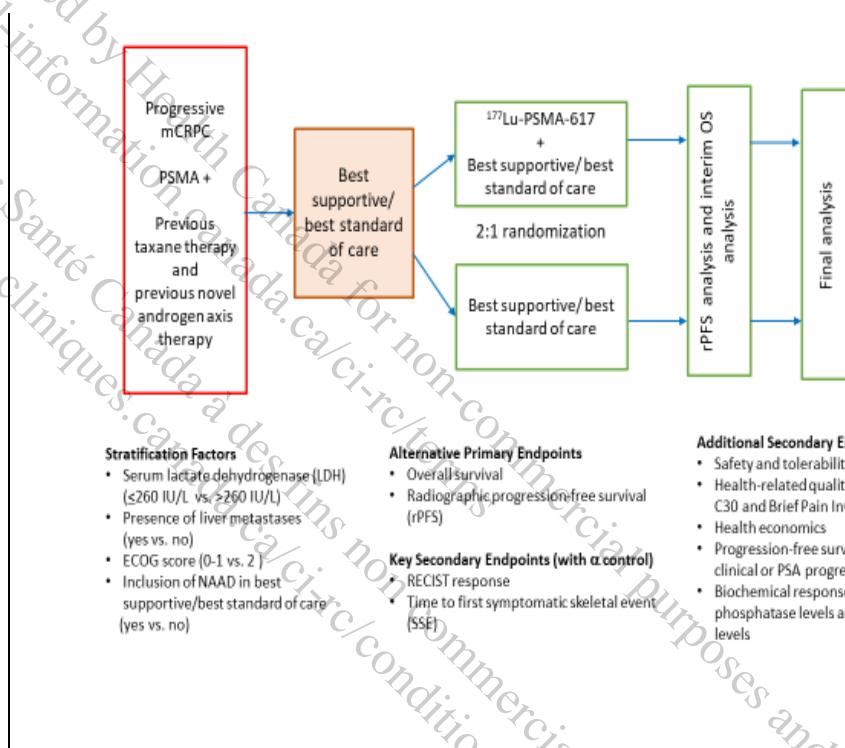
|
Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 26 of 112

addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).



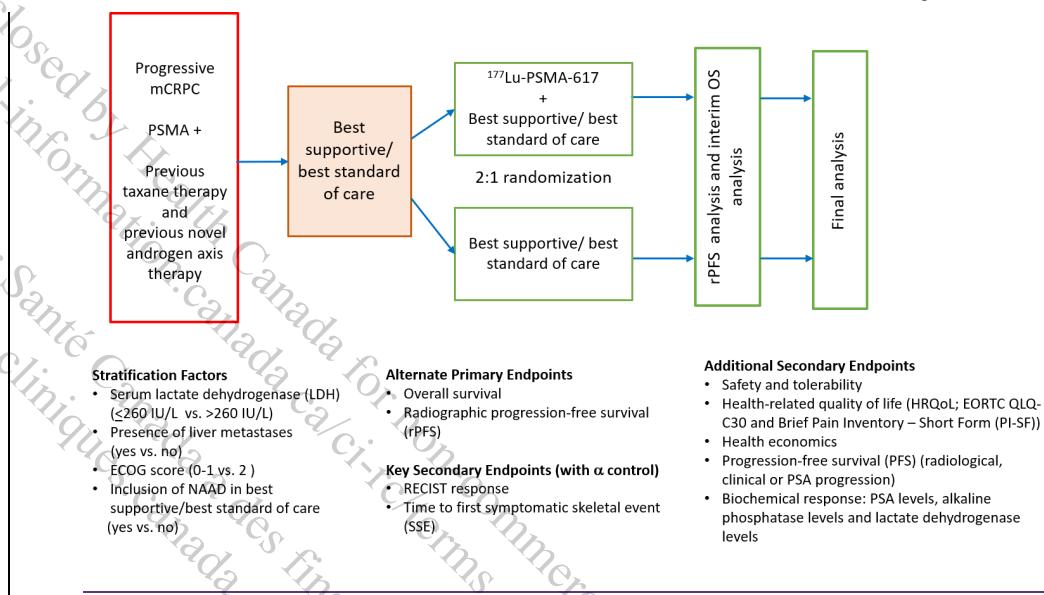


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and

Page 28 of 112

- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue the treatment part of the study at any time. If a patient withdraws consent for the treatment part of the study, the patient will continue to be followed for long term follow up unless they specifically withdraw for the long term follow up of the study.

An End of Treatment (EOT) visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of survival and treatment updatesinformation about new treatments, along with the patient's response to these treatments, adverse events assessment, as well as blood for and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for up to 24 months or until 489 deaths have occurred. If a patient withdraws

Patients who withdraw their consent from to participate in the treatment portion of the study, they will or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked to confirm if they will for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent to all aspects detailing what kind of long term follow up, survival only or no long term assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up activity status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 750 patients involving about 110 sites worldwide.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternative/alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ¹⁷⁷Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100

Page 30 of 112

patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ¹⁷⁷Lu-PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

¹⁷⁷Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 2442 publications, summarizing the safety and or efficacy information from over 500800 subjects. Across these studies doses have ranged from 21.1-12.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-89 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However, efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ¹⁷⁷Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018), Kulkarni et al 2018, Bräuer et al 2017, Yordanova et al 2017). In addition, a recent review suggests optimal dosing of 6 cycles of ¹⁷⁷Lu-PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ¹⁷⁷Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ¹⁷⁷Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ¹⁷⁷Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 31 of 112

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or best supportive/best standard of care (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period.

Total duration of the trial for randomized patients, considering expected survival, is expected to be 19 to 23 months, including a 1-month screening period, 6 to 10-month treatment period and a long-term follow-up period for safety and survival lasting up to 24 months or at least until 489 deaths have occurred. Total duration of the study, from first date of randomization to last follow-up, will be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 489 deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1 and Section 8.7.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. Participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 32 of 112

5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{be} ⁶⁸Ga-PSMA-11 PET/CT scan, positive, and eligible as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient is not willing to receive a second taxane regimen, or
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation ~~or~~, intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum/plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesion(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
 - a. Bone marrow reserve:
 - White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 33 of 112

- Platelets $\geq 100 \times 10^9/\text{L}$ ($100 \times 10^9/\text{L}$ is equivalent to $100 \times 10^3/\mu\text{L}$ and $100 \times \text{K}/\mu\text{L}$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu\text{L}$)
- Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

b. Hepatic:

- Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

c. Renal:

- Serum/plasma creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$

15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L)

[Inclusion #16 has been removed]

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

For patients who have partners of childbearing potential:

18. Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 6 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:

- a. Are allowed by the protocol
- b. Have been agreed to by the treating investigator and patient
- c. Allow for the management of the patient without $^{177}\text{Lu-PSMA-617}$

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization:
Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.

Page 34 of 112

5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion within 30 days of randomization for the sole purpose of eligibility making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient only withdraws consent for the treatment part of the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety and survival follow-up ~~or~~. This may include blood work results, radiographic follow up and information about new treatments and his response to these treatments. Patients may also choose to be followed for survival only long-term follow up.

This trial design is intent to treat so that all subjects will be followed for up to 24 months for safety and survival or until 489 deaths have occurred. The total of 489 deaths are expected to have occurred approximately 15 months after the last patient has been randomized.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January01

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ⁶⁸Ga-PSMA-11

For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure. The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

5.1.2 Administration of ¹⁷⁷Lu-PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ¹⁷⁷Lu-PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ¹⁷⁷Lu-PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ¹⁷⁷Lu-PSMA-617 administration.

¹⁷⁷Lu-PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(+/- 5) minutes before and at 30(+/- 5) and 60(+/- 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ¹⁷⁷Lu-PSMA-617 administration should be recorded.

A decision to order ¹⁷⁷Lu-PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ¹⁷⁷Lu-PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 36 of 112

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count <3.0 $\times 10^9/\text{L}$• ANC <1.5 $\times 10^9/\text{L}$	$\geq\text{Grade } 2$	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematologic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Thrombocytopenia (platelet count of < 75 x 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Transfusions may be given as clinically indicated for thrombocytopenia.
Hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Serum/plasma creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (not amenable to medical intervention)	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
-------	-------	----------------------------

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only.

Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 812 weeks.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm should be administered as per physician's orders and protocol at the institution, and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization or shortly thereafter. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

Page 39 of 112

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must remainmaintain castrate and receive a luteinizing hormone releasing hormone analogue (agonist)levels of serum/plasma testosterone either by chemical castration or antagonist) or polystyrene phosphate throughout the studyby having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Page 40 of 112

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

If a patient discontinues the treatment part of the study for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum/ <u>plasma</u> testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks (+ 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. PSMAStudy eligibility <u>based on PSMA positivity</u> will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT= computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

Page 43 of 112

6.2.3 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.4 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.5 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as

Page 44 of 112

global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies (Cella et al 1993, Esper et al 1997)
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format (Webster et al 2003)

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.6 Health Economics

A health economics (HE) sub-study will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.7 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.8 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum/[plasma](#) testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry

- Sodium
- potassium
- total and direct bilirubin
- ALP
- AST
- ALT
- LDH
- blood urea nitrogen**
- creatinine
- uric acid
- phosphorus
- chloride
- bicarbonate*
- calcium
- glucose
- total protein
- albumin

*total carbon dioxide or equivalent is acceptable

** urea is acceptable

Urinalysis

- urine pH
- protein content
- specific gravity
- appearance and color
- glucose
- ketones

Hematology

- complete blood count (white blood cell count and differential)
- red blood cell count
- hemoglobin
- hematocrit
- platelet count

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (eg, condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 6 months following the last dose of ¹⁷⁷Lu-PSMA-617.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect self-reported, long term follow up specific AE assessments, and survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work [results](#) will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study [or come off the treatment portion of the study for any reason other than radiographic disease progression](#) will be asked for permission to continue long-term status updates: [which may include, in addition to the above, collection of radiographic images \(bone scans and CT scans and/or MRIs\).](#)

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

[For any of these patients who are unable to sign the second consent \(i.e. does not return to the site, etc.\) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.](#)

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Page 47 of 112

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Progression of disease is not considered an AE or SAE for this study.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended response to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death; except for deaths due to progression of disease• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event.

7.2 Evaluating and recording adverse events

All adverse events (AEs) will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the last dose or intervention identified as best supportive/best standard of care, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of

Page 48 of 112

care-; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is “unknown and of questionable relationship to the study drug” the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is “unknown but not related to the study drug” the determination and rationale will be documented in the patient’s case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

All statistical analyses will be carried out using SAS version 9.3 (or later). The SAP will be written and finalized prior to the first planned analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 750 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 13 months, a total of 750 patients randomized is expected to yield (i) 457 rPFS events and 249 deaths with a minimum follow-up of 3-4 months after the last patient is randomized and (ii) 489 death events with a minimum follow-up of 15 months after the last patient is randomized. Central independent assessments will be used to determine rPFS events.

The analyses of rPFS and OS are event driven. The analysis of rPFS is planned with 457 events with an allocated 1-sided alpha level of 0.001. An interim analysis of OS is planned to coincide with this analysis of rPFS at which time 249 deaths are expected; the allocated 1-sided alpha

Page 50 of 112

level for OS at the interim will be 0.001. A final analysis of OS will take place with 489 deaths which are expected to have accrued with 15 months follow-up post the last patient randomized. The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if both achieve $p < 0.001$ 1-sided, then the alpha level for the final analysis of OS will be 0.025 1-sided.
- if only one reaches $p < 0.001$ 1-sided, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if neither reaches $p < 0.001$ 1-sided, then the alpha level for the final analysis of OS will be 0.023 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; overall power is at least 91.4% and the overall Type I error rate is ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.001$ for rPFS and the interim analysis of OS are 0.736 and 0.660 respectively; and the observed HR that will meet $p < 0.023$ to $p < 0.025$ in the final analysis of OS are 0.826 to 0.829.

8.2 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. Patient efficacy data in this dataset will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ^{68}Ga -PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.3 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.4 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January 01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 51 of 112

- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.5 Efficacy analyses

8.5.1 Alternate primary endpoint efficacy analysis

8.5.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. The analysis of rPFS is event driven and will take place once 457 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.001 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified Cox proportional hazards regression model will be used to analyze rPFS in the FAS dataset. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors. The HR (active: control), its 95% confidence interval, and the associated 1-sided p-value will be presented. A supportive analysis will be provided via a stratified log-rank test, stratifying again for the randomization stratification factors.

8.5.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 457 rPFS events); it is anticipated that approximately 249 deaths will have accrued at the time of the rPFS analysis. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 489 deaths have occurred. As described in Section 8.1, the allocated alpha level for the final OS analysis will be between 0.023 and 0.0251-sided, depending on the results of the earlier rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed in the same manner as rPFS.

|
Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January01

8.5.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level or OS to meet its allocated alpha level at either (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) or (ii) at the final OS analysis with 489 deaths.

Alpha allocation and recycling is used to ensure control of the overall Type I error rate as described in Section 8.1.

8.5.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

Time to SSE will be analyzed using a Cox regression model in the same manner as described for the alternate primary endpoints. Objective response and disease control rate will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints are:

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.

Page 53 of 112

5. Biochemical response endpoints:

- d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints (e.g. PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for the alternate primary endpoints except using a 2-sided p-value. Disease control rate DCR will be analyzed in the same manner as objective response rate and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.6 Safety analyses

8.6.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.6.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga -PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga -PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ^{68}Ga -PSMA-11 dosing up to 6 days after the date of ^{68}Ga -PSMA-11 dosing as long as prior to the first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ^{68}Ga -PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ^{68}Ga -PSMA-11 TEAEs. Unrelated ^{68}Ga -PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Page 54 of 112

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.6.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.6.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.7 IDMC and Interim Data Evaluation

8.7.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS at 457 events, interim OS at the time of the rPFS analysis and final OS with 489 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.7.2 Formal Interim Analysis of OS

As described above in Section 8.1, one formal interim analysis is planned for OS to take place at the time of the rPFS analysis. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 489 OS events have accrued at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical

Page 56 of 112

study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

|
| Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January01

Page 57 of 112

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician

|
Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 58 of 112

appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 59 of 112

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

|
| Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

14. REFERENCES

Ahmadzadehfar et al 2016

Ahmadzadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmadzadehfar et al 2015

Ahmadzadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015, 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bräuer et al 2017

Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ¹⁷⁷Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2017 Sep;44(10):1663-70.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Page 61 of 112

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

Page 62 of 112

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ¹⁷⁷Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [¹⁷⁷Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Page 63 of 112

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Clin Oncol. 2019;37(suppl 7S): 228.

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research. 2018 Jul;78(13):CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987-88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807-1812. doi:10.1093/annonc/mdt136

Page 64 of 112

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With ^{177}Lu -PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of ^{177}Lu -PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating ^{177}Lu -PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flehsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print]

Page 65 of 112

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 66 of 112

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ¹⁷⁷Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017;DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesely S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 67 of 112

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January01

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^a	X					X
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum/plasma testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit.					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. [Can be completed up to 3 days prior to Day 1.](#)

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no.: 23.0

Endocyte, Inc.
16 January 01 April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 69 of 112

Table 4 Schedule of assessments:¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

| Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6***	End of Treatment ^g	Long - term follow-up
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Cycle Week:							Every 812 weeks $(\pm 1\text{ week})$ $(\pm 4\text{ days})$		Every 3 months $(\pm 1\text{ month})$
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X				X ^a		X ^a	X	•
AE monitoring ^b	X			X ^a		X ^a	X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	

Protocol no. PSMA-617-01
Version no.: 23.0

Endocyte, Inc.
16 January 01 April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 71 of 112

BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
--------	------------------	--	--	--	--	--	------------------	----------------	--

| Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 72 of 112

Administer ¹⁷⁷ Lu-PSMA-617	X								Co lle ct: • • • •
---------------------------------------	---	--	--	--	--	--	--	--	--------------------------------------

| Protocol no. PSMA-617-01
Version no. 23.0

| This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 73 of 112

*Document released under the Access to Information Act
Document divulgué en vertu de la Loi sur l'accès à l'information*

This document is provided by Health Canada for non-commercial purposes and subject to the Terms and Conditions of Use available at www.hc-sc.gc.ca/ci-rc/terms.

Ce document est fourni par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation disponibles à l'adresse www.hc-sc.gc.ca/ci-rc/conditions.

Protocol no. PSMA-617-01
Version no.: 23.0

16 January 01 April 2011

Page 74 of 112

Protocol no. PSMA-617-01
Version no.: 23.0

16 January01 April 201

Page 75 of 112

--	--	--	--	--	--	--	--	--

Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 76 of 112

--	--	--	--	--	--	--	--	--	--	--	--

Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 77 of 112

Best supportive/ best standard of care	As per physician's orders						As per physician's orders	
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X
Serum/plasma testosterone	X ^c						X ^c	X
PSA	X ^c						X ^c	X
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of ¹⁷⁷ Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the end of treatment visit							

Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

* After the Cycle 4 dose of ¹⁷⁷Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.

b Adverse event monitoring will commence at time of consent.

c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 28²⁹.

d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30(+/-5) -minutes post, and 60(+/-5) -minutes post ¹⁷⁷Lu-PSMA-617 administration.

e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 8-12 weeks (+/- 4 days).

g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study

h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum/plasma testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after Cycle 1 Day 1 ^g for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will commence at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. [Can be completed up to 3 days prior to Day 1.](#)

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker-[or](#) clinician [or site research team member](#).

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^f Treatment ^g	Long - ter m fol lo w-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			Ev ery 3 m onths (\pm 1 m onth)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Co llect: •
Concomitant medication review	X			X ^a			X*	X	
AE monitoring ^b	X		X ^a		X ^a		X*	X	
Weight	X ^b X ^c						X ^b X ^c	X	
ECOG	X ^b X ^c						X ^b X ^c	X	
Directed physical exam	X ^b X ^c						X ^b X ^c	X	
Vital signs ^e signs ^d	X ^b X ^c						X ^b X ^c	X	
EQ-5D-5L	X ^{d,g} X ^{e,h}						X ^{d,g} X ^{e,h}	X ^{d,g} X ^{e,h}	
FACT-P	X ^{d,g} X ^{e,h}						X ^{d,g} X ^{e,h}	X ^{d,g} X ^{e,h}	
BPI-SF	X ^{d,g} X ^{e,h}						X ^{d,g} X ^{e,h}	X ^{d,g} X ^{e,h}	

Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 81 of 112

Protocol no. PSMA-617-01
Version no.: 23.0

16 January 01 April 2015

Page 82 of 112

Information Canada à des fins non commerciales et sous réserve d'être utilisée par Santé Canada pour des fins non commerciales et sous réserve d'être utilisée par Santé Canada for non-commercial purposes and subject to the Terms and Conditions of Use at www.hc-sc.gc.ca/ci-rc/terms

Protocol no. PSMA-617-01
Version no.: 23.0

16 January01 April 201

Page 83 of 112

•

| Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 84 of 112

Protocol no. PSMA-617-01
Version no.: 23.0

16 January01 April 201

Page 85 of 112

--	--	--	--	--	--	--	--	--	--	--	--

Protocol no. PSMA-617-01
Version no. 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01 April 2019

Page 86 of 112

Best supportive/best standard of care									
Hematology ^a	X ^b X ^c		X ^b X ^c		X ^b X ^c		X ^b	X	
Chemistry ^d	X ^b X ^c		X ^b X ^c		X ^b X ^c		X ^b	X	
Serum/plasma testosterone	X ^b X ^c						X ^b	X	
PSA	X ^b X ^c						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after Cycle 1 Day 1 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the end of treatment visit								

^a Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

Protocol no. PSMA-617-01
Version no. 23.0

Endocyte, Inc.
16 January 01 April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- ^a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
- ^b Adverse event monitoring will commence at time of consent.
- ^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- ^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
- ^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- ^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 8 every 12 weeks (\pm 1 week 4 days).
- ^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose or intervention of best supportive/best standard of care; but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
- ^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Page 88 of 112

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ¹⁷⁷Lu-PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ¹⁷⁷Lu-PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ¹⁷⁷Lu-PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ¹⁷⁷Lu-PSMA-617 therapy

Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 01

Page 89 of 112

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

|
| Protocol no. PSMA-617-01
Version no.: 23.0
April 2019

Endocyte, Inc.
16 January01

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 90 of 112

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Page 91 of 112

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191-205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 92 of 112

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Protocol no. PSMA-617-01
Version no.: 22.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
~~16 January 2019~~ 01 April 2019

Page 93 of 112

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

| Protocol no. PSMA-617-01
Version no.: 22.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 2019

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">• Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug• Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression• Ignore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve endpoints:</p> <ul style="list-style-type: none">• Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">• Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">• PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve endpoints:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">• Record up to 5 lesions per site of disease• Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately• Only report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baseline• Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately• Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimension• Record complete elimination of disease at any site separately• Confirm favorable change with second scan• Record changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">• Record changes in nodal and visceral disease separately• Record up to 5 lesions per site of spread• Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)• Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Page 95 of 112

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">Record outcome as new lesions, no new lesions or resolved lesion • <p>First scheduled reassessment:</p> <ul style="list-style-type: none">No new lesions: continue therapyNew lesions: perform a confirmatory scan 6 or more weeks later • <p>Confirmatory scan:</p> <ul style="list-style-type: none">No new lesions: continue therapyAdditional new lesions: progression • <p>Subsequent scheduled reassessments:</p> <ul style="list-style-type: none">No new lesions: continueNew lesions: progression <p>• Changes in intensity or uptake do not constitute regression or progression For prevent/delay end points (progression):</p> <ul style="list-style-type: none">Exclude pseudoprogression in the absence of symptoms or other signs of progressionAt least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documentedFor scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scanDate of progression is the date of the scan that first documents the second lesionChanges in intensity of uptake alone do not constitute either progression or regressionReport the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 96 of 112

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 2019 01 April 2019

Page 97 of 112

Brief Pain Inventory (Short Form)

Time: ____ : ____ AM PM
Today's Date (day, month, year):

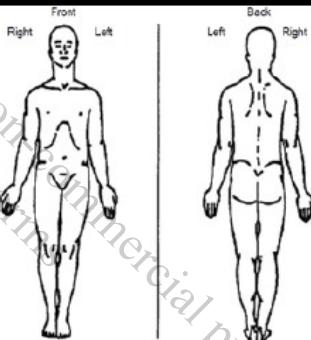
Today's Date (day, month, year)
JAN □ JAN □ MAR □ MAY □ MAY □ JUL □ SEP □ NOV □ NOV
□ Day - FEB □ FEB □ APR □ JUN □ JUN □ AUG □ AUG □ OCT □ OCT □ DEC
□ Month -

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.



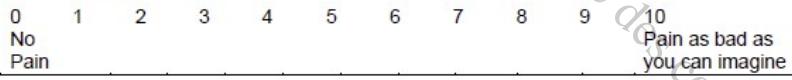
4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.



5. Please rate your pain by circling the one number that best describes your pain on the average.



6. Please rate your pain by circling the one number that best describes how much pain you have right now.



Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

16 January 01 April 2019

Page 98 of 112

Today's Date (Day, Month, Year): <input type="text"/> DAY <input type="text"/> MONTH <input type="text"/> YEAR (Example: 08-FEB-2016)											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 2019

Page 99 of 112

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (sample only, not for patient use)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 22.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 2019 01 April 2019

Page 100 of 112



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
16 January 2019 01 April 2019

Page 101 of 112

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
-
- I have slight problems in walking about
-
- I have moderate problems in walking about
-
- I have severe problems in walking about
-
- I am unable to walk about
-

SELF-CARE

- I have no problems washing or dressing myself
-
- I have slight problems washing or dressing myself
-
- I have moderate problems washing or dressing myself
-
- I have severe problems washing or dressing myself
-
- I am unable to wash or dress myself
-

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
-
- I have slight problems doing my usual activities
-
- I have moderate problems doing my usual activities
-
- I have severe problems doing my usual activities
-
- I am unable to do my usual activities
-

PAIN / DISCOMFORT

- I have no pain or discomfort
-
- I have slight pain or discomfort
-
- I have moderate pain or discomfort
-
- I have severe pain or discomfort
-
- I have extreme pain or discomfort
-

ANXIETY / DEPRESSION

- I am not anxious or depressed
-
- I am slightly anxious or depressed
-
- I am moderately anxious or depressed
-
- I am severely anxious or depressed
-
- I am extremely anxious or depressed
-

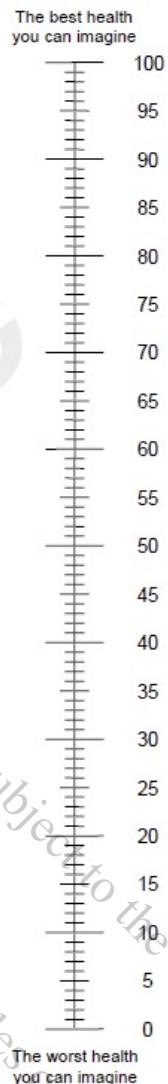
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 102 of 112

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

16 January 2019 01 April 2019

Page 103 of 112

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy -
Prostate) (sample only, not for patient use)**

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 22.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
~~16 January 2019~~ 01 April 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

GP1
GP2
GP3
GP4
GP5
GP6
GP7

		Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4	
I have nausea	0	1	2	3	4	
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4	
I have pain	0	1	2	3	4	
I am bothered by side effects of treatment	0	1	2	3	4	
I feel ill	0	1	2	3	4	
I am forced to spend time in bed	0	1	2	3	4	

SOCIAL/FAMILY WELL-BEING

GS1
GS2
GS3
GS4
GS5
GS6
Q1
GS7

		Not at all	A little bit	Some-what	Quite a bit	Very much
I feel close to my friends	0	1	2	3	4	
I get emotional support from my family	0	1	2	3	4	
I get support from my friends	0	1	2	3	4	
My family has accepted my illness	0	1	2	3	4	
I am satisfied with family communication about my illness	0	1	2	3	4	
I feel close to my partner (or the person who is my main support)	0	1	2	3	4	
<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>						
I am satisfied with my sex life	0	1	2	3	4	

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNs</u>	Not at all	A little bit	Somewhat	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 107 of 112

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 23.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
~~16 January 2019~~ 01 April 2019

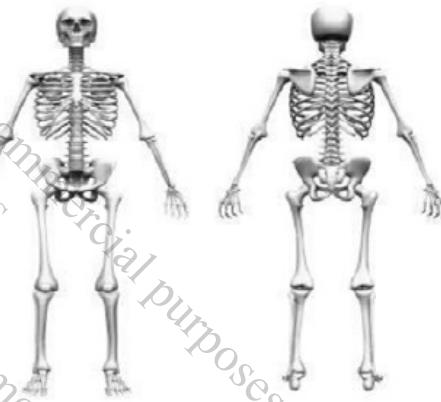
Page 108 of 112

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 109 of 112

Week 8 BASELINE Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input checked="" type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ? <input type="checkbox"/> Yes* <input type="checkbox"/> No	
* Presence of new lesions at this time does not confirm progression	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed): 	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

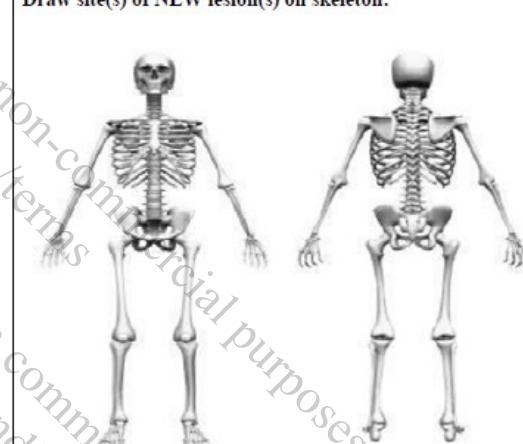
Page 110 of 112

Week 16 Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

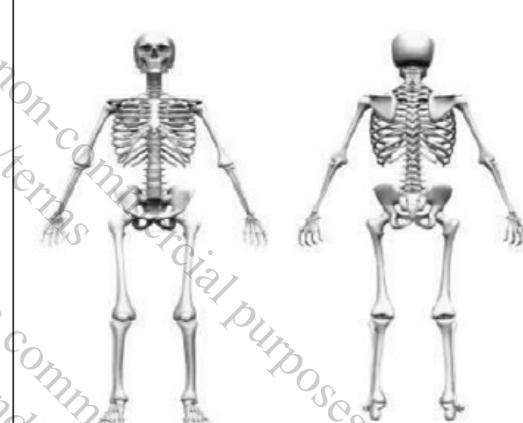
Page 111 of 112

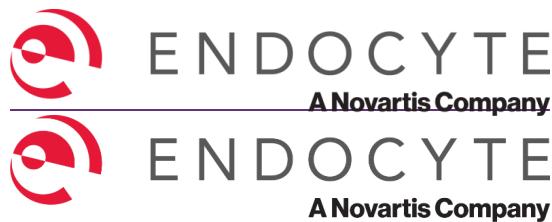
Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date:	<p>DD-MM-YY</p>
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 112 of 112

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date:	<p>DD-MM-YY</p>
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (MCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 34.0

Date: 01 April 2019

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)
133,925 or site equivalent (⁶⁸Ga-PSMA-11)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617; ⁶⁸Ga-PSMA-11

Sponsor: Endocyte, Inc., A Novartis Company
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Page 2 of 101

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Protocol No./Acronym: *from Title page*
Version No.: *from Title page*

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 3 of 101

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Protocol no. PSMA-617-01
Version no.: 240
July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company
01 April 08

Table of Contents

Site Principal Investigator Signature	3
Table of Contents	4
Revision History	12
Clinical Trial Summary	14
List of Abbreviations and Definitions	17
1. Introduction	19
1.1 Background information	19
1.2 Summary of nonclinical studies with clinical significance	23
1.3 Summary of known and potential risks and benefits	24
2. Trial Objectives and Endpoints	25
2.1 Trial objectives	25
2.1.1 Primary objective	25
2.1.2 Key secondary objectives	25
2.1.3 Additional secondary objectives	25
2.2 Trial endpoints	25
2.2.1 Alternate Primary endpoints	25
2.2.2 Key Secondary endpoints	26
2.2.3 Additional Secondary endpoints	26
3. Trial Design	27
3.1 Overview of the clinical trial design	27
3.2 Rationale for the study design	30
3.3 Measures taken to minimize/avoid bias	30
3.4 Description of the clinical trial	31
3.4.1 Description of investigational medicinal product	31
3.4.2 Dosage and rationale for dose selection	31
3.4.3 Subject allocation to treatment	32
3.4.4 End of treatment visit	32
3.4.5 Duration of Subject Participation	32
3.5 End of trial definition	33
4. Selection and Withdrawal of Subjects	33
4.1 Inclusion criteria	33
4.2 Exclusion criteria	35
4.3 Subject withdrawal of consent for study or treatment	36
5. Treatment of Subjects	36
5.1 Treatment with the investigational medicinal product	36

Page 5 of 101

5.1.1	Administration of ⁶⁸ Ga PSMA-11	36
5.1.2	Administration of ¹⁷⁷ Lu PSMA-617	37
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu PSMA-617 injections	37
5.1.4	Management of toxicity adverse events: dosing delays and modification	38
5.2	Best supportive/best standard of care	39
5.3	Concomitant medications/ supportive care	40
5.3.1	Permitted concomitant medications/ supportive care	40
5.3.2	Prohibited concomitant medications	41
5.4	Monitoring treatment compliance	41
5.5	Treatment discontinuation	41
6.	Study Assessments and Procedures	41
6.1	Screening procedures and baseline assessments	41
6.2	Efficacy assessments	43
6.2.1	Radiographic imaging for tumor assessments	44
6.2.2	RECIST criteria	44
6.2.3	Symptomatic skeletal events	44
6.2.4	Pain score	44
6.2.5	Health related quality of life	45
6.2.6	Health Economics	46
6.2.7	Clinical progression	46
6.2.8	PSA levels	46
6.3	Safety assessments	47
6.3.1	Clinical laboratory evaluations	47
6.3.2	Vital signs	47
6.3.3	Electrocardiograms	47
6.3.4	Birth Control	47
6.4	End of treatment visit procedures	47
6.5	Long term follow up procedures	48
7.	Adverse Events	48
7.1	Adverse event definitions	48
7.2	Evaluating and recording adverse events	49
7.3	Immediate Adverse Event Reporting	50
7.3.1	Serious Adverse Events	50
7.3.2	Serious adverse event subject follow up	50
7.3.3	Sponsor Contact Information for Immediate Reporting	51
8.	Statistics	51

Page 6 of 101

8.1	Sample size and power determination	52
8.2	Analysis populations	53
8.3	Demographics and baseline disease characteristics	53
8.4	Patient disposition	54
8.5	Efficacy analyses	54
8.5.1	Alternate primary endpoint efficacy analysis	54
8.5.2	Secondary efficacy analyses	55
8.6	Safety analyses	57
8.6.1	Extent of exposure	57
8.6.2	Analysis of adverse events	57
8.6.3	Analysis of laboratory assessments	57
8.6.4	Analysis of vital sign data	58
8.7	IDMC and Interim Data Evaluation	58
8.7.1	IDMC	58
8.7.2	Formal Interim Analysis of OS	58
9.	Access to Source Data/Documents	58
10.	Ethics	59
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	59
10.2	Informed consent	59
10.3	Health Insurance Portability and Accountability Act	59
10.4	Confidentiality	60
11.	Compliance and quality control	60
11.1	Compliance with Monitoring and Audits	60
12.	Data Handling, Record Keeping, and Compliance	61
12.1	Investigational medicinal product accountability	61
12.2	Breaking the blind	61
12.3	Data collection forms and source document identification	61
12.4	Record maintenance and retention	61
12.5	Archiving	62
13.	Publication Policy	62
14.	References	63
Appendix 1	Schedules of Assessments	70
Appendix 2	Suggested treatment guidelines	77
Appendix 3	Principal Investigator Signature	78
Appendix 4a	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	79

Page 7 of 101

Appendix 4b — Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....	80
Appendix 5 — Common Terminology Criteria for Adverse Events	81
Appendix 6 — Response Evaluation Criteria in Solid Tumors	82
Appendix 7 — Prostate Cancer Working Group 3 Recommendations	83
Appendix 8 — BPI SF (<i>sample only, not for patient use</i>)	85
Appendix 9 — EQ 5D-5L (European Quality of Life (EuroQol) -5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	88
Appendix 10 — FACT P (Functional Assessment of Cancer Therapy -Prostate) (<i>sample only, not for patient use</i>)	92
Appendix 11 — PCCTC Bone Scan Assessment Tool	96
<u>Site Principal Investigator Signature</u>	<u>3</u>
<u>Table of Contents</u>	<u>4</u>
<u>Revision History</u>	<u>12</u>
<u>Clinical Trial Summary</u>	<u>14</u>
<u>List of Abbreviations and Definitions</u>	<u>17</u>
<u>1. Introduction</u>	<u>19</u>
<u>1.1 Background information</u>	<u>19</u>
<u>1.2 Summary of nonclinical studies with clinical significance</u>	<u>23</u>
<u>1.3 Summary of known and potential risks and benefits</u>	<u>24</u>
<u>2. Trial Objectives and Endpoints</u>	<u>25</u>
<u>2.1 Trial objectives</u>	<u>25</u>
<u>2.1.1 Primary objective</u>	<u>25</u>
<u>2.1.2 Key secondary objectives</u>	<u>25</u>
<u>2.1.3 Additional secondary objectives</u>	<u>25</u>
<u>2.2 Trial endpoints</u>	<u>25</u>
<u>2.2.1 Alternate Primary endpoints</u>	<u>25</u>
<u>2.2.2 Key Secondary endpoints</u>	<u>26</u>
<u>2.2.3 Additional Secondary endpoints</u>	<u>26</u>
<u>3. Trial Design</u>	<u>27</u>
<u>3.1 Overview of the clinical trial design</u>	<u>27</u>
<u>3.1.1 Study design update</u>	<u>30</u>
<u>3.2 Rationale for the study design</u>	<u>30</u>
<u>3.3 Measures taken to minimize/avoid bias</u>	<u>30</u>
<u>3.4 Description of the clinical trial</u>	<u>31</u>
<u>3.4.1 Description of investigational medicinal product</u>	<u>31</u>
<u>3.4.2 Dosage and rationale for dose selection</u>	<u>31</u>

Page 8 of 101

<u>3.4.3</u>	<u>Subject allocation to treatment.....</u>	<u>32</u>
<u>3.4.4</u>	<u>End of treatment visit</u>	<u>32</u>
<u>3.4.5</u>	<u>Duration of Subject Participation.....</u>	<u>32</u>
<u>3.5</u>	<u>End of trial definition</u>	<u>33</u>
<u>4.</u>	<u>Selection andDISCONTINUATION of Subjects.....</u>	<u>33</u>
<u>4.1</u>	<u>Inclusion criteria.....</u>	<u>33</u>
<u>4.2</u>	<u>Exclusion criteria.....</u>	<u>35</u>
<u>4.3</u>	<u>Subject withdrawal of consent for study or treatment.....</u>	<u>36</u>
<u>5.</u>	<u>Treatment of Subjects.....</u>	<u>36</u>
<u>5.1</u>	<u>Treatment with the investigational medicinal product</u>	<u>36</u>
<u>5.1.1</u>	<u>Administration of ⁶⁸Ga-PSMA-11</u>	<u>36</u>
<u>5.1.2</u>	<u>Administration of ¹⁷⁷Lu-PSMA-617</u>	<u>37</u>
<u>5.1.3</u>	<u>Toxicity risk reduction and supportive care for ¹⁷⁷Lu-PSMA-617 injections ..</u>	<u>37</u>
<u>5.1.4</u>	<u>Management of toxicity adverse events: dosing delays and modification.....</u>	<u>38</u>
<u>5.2</u>	<u>Best supportive/best standard of care.....</u>	<u>39</u>
<u>5.3</u>	<u>Concomitant medications/ supportive care</u>	<u>40</u>
<u>5.3.1</u>	<u>Permitted concomitant medications/ supportive care</u>	<u>40</u>
<u>5.3.2</u>	<u>Prohibited concomitant medications</u>	<u>41</u>
<u>5.4</u>	<u>Monitoring treatment compliance</u>	<u>41</u>
<u>5.5</u>	<u>Treatment discontinuation.....</u>	<u>41</u>
<u>6.</u>	<u>Study Assessments and Procedures.....</u>	<u>41</u>
<u>6.1</u>	<u>Screening procedures and baseline assessments</u>	<u>41</u>
<u>6.2</u>	<u>Efficacy assessments</u>	<u>43</u>
<u>6.2.1</u>	<u>Radiographic imaging for tumor assessments</u>	<u>44</u>
<u>6.2.2</u>	<u>Additional Imaging Analyses.....</u>	<u>44</u>
<u>6.2.3</u>	<u>RECIST criteria.....</u>	<u>44</u>
<u>6.2.4</u>	<u>Symptomatic skeletal events.....</u>	<u>44</u>
<u>6.2.5</u>	<u>Pain score</u>	<u>44</u>
<u>6.2.6</u>	<u>Health-related quality of life</u>	<u>45</u>
<u>6.2.7</u>	<u>Health Economics</u>	<u>46</u>
<u>6.2.8</u>	<u>Clinical progression</u>	<u>46</u>
<u>6.2.9</u>	<u>PSA levels.....</u>	<u>46</u>
<u>6.3</u>	<u>Safety assessments.....</u>	<u>47</u>
<u>6.3.1</u>	<u>Clinical laboratory evaluations</u>	<u>47</u>
<u>6.3.2</u>	<u>Vital signs</u>	<u>47</u>
<u>6.3.3</u>	<u>Electrocardiograms</u>	<u>47</u>
<u>6.3.4</u>	<u>Birth Control</u>	<u>47</u>

Protocol no. PSMA-617-01

Version no.: 34.0

July 2019

Endocyte, Inc., a Novartis Company

01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 9 of 101

<u>6.4</u>	<u>End of treatment visit procedures.....</u>	<u>47</u>
<u>6.5</u>	<u>Long-term follow-up procedures.....</u>	<u>48</u>
<u>7.</u>	<u>Adverse Events.....</u>	<u>48</u>
<u>7.1</u>	<u>Adverse event definitions.....</u>	<u>48</u>
<u>7.2</u>	<u>Evaluating and recording adverse events</u>	<u>49</u>
<u>7.3</u>	<u>Immediate Adverse Event Reporting</u>	<u>50</u>
<u>7.3.1</u>	<u>Serious Adverse Events</u>	<u>50</u>
<u>7.3.2</u>	<u>Serious adverse event subject follow-up.....</u>	<u>50</u>
<u>7.3.3</u>	<u>Sponsor Contact Information for Immediate Reporting</u>	<u>51</u>
<u>8.</u>	<u>Statistics.....</u>	<u>51</u>
<u>8.1</u>	<u>Revision to the protocol and statistical analyses of rPFS and OS</u>	<u>51</u>
<u>8.2</u>	<u>Revisions to planned analyses</u>	<u>51</u>
<u>8.3</u>	<u>Sample size and power determination</u>	<u>52</u>
<u>8.4</u>	<u>Analysis populations</u>	<u>53</u>
<u>8.5</u>	<u>Demographics and baseline disease characteristics</u>	<u>53</u>
<u>8.6</u>	<u>Patient disposition</u>	<u>54</u>
<u>8.7</u>	<u>Efficacy analyses</u>	<u>54</u>
<u>8.7.1</u>	<u>Alternate primary endpoint efficacy analysis</u>	<u>54</u>
<u>8.7.2</u>	<u>Secondary efficacy analyses</u>	<u>55</u>
<u>8.8</u>	<u>Safety analyses</u>	<u>57</u>
<u>8.8.1</u>	<u>Extent of exposure</u>	<u>57</u>
<u>8.8.2</u>	<u>Analysis of adverse events</u>	<u>57</u>
<u>8.8.3</u>	<u>Analysis of laboratory assessments.....</u>	<u>57</u>
<u>8.8.4</u>	<u>Analysis of vital sign data</u>	<u>58</u>
<u>8.9</u>	<u>IDMC and Interim Data Evaluation</u>	<u>58</u>
<u>8.9.1</u>	<u>IDMC</u>	<u>58</u>
<u>8.9.2</u>	<u>Formal Interim Analysis of OS</u>	<u>58</u>
<u>9.</u>	<u>Access to Source Data/Documents.....</u>	<u>58</u>
<u>10.</u>	<u>Ethics</u>	<u>59</u>
<u>10.1</u>	<u>Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB).....</u>	<u>59</u>
<u>10.2</u>	<u>Informed consent</u>	<u>59</u>
<u>10.3</u>	<u>Health Insurance Portability and Accountability Act.....</u>	<u>59</u>
<u>10.4</u>	<u>Confidentiality.....</u>	<u>60</u>
<u>11.</u>	<u>Compliance and quality control.....</u>	<u>60</u>
<u>11.1</u>	<u>Compliance with Monitoring and Audits</u>	<u>60</u>
<u>12.</u>	<u>Data Handling, Record Keeping, and Compliance</u>	<u>61</u>

Page 10 of 101

<u>12.1</u>	<u>Investigational medicinal product accountability.....</u>	<u>61</u>
<u>12.2</u>	<u>Breaking the blind</u>	<u>61</u>
<u>12.3</u>	<u>Data collection forms and source document identification</u>	<u>61</u>
<u>12.4</u>	<u>Record maintenance and retention</u>	<u>61</u>
<u>12.5</u>	<u>Archiving</u>	<u>62</u>
<u>13.</u>	<u>Publication Policy.....</u>	<u>62</u>
<u>14.</u>	<u>References</u>	<u>63</u>
<u>Appendix 1</u>	<u>Schedules of Assessments</u>	<u>70</u>
<u>Appendix 2</u>	<u>Suggested treatment guidelines</u>	<u>77</u>
<u>Appendix 3</u>	<u>Principal Investigator Signature</u>	<u>78</u>
<u>Appendix 4a</u>	<u>Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....</u>	<u>79</u>
<u>Appendix 4b</u>	<u>Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....</u>	<u>80</u>
<u>Appendix 5</u>	<u>Common Terminology Criteria for Adverse Events</u>	<u>81</u>
<u>Appendix 6</u>	<u>Response Evaluation Criteria in Solid Tumors</u>	<u>82</u>
<u>Appendix 7</u>	<u>Prostate Cancer Working Group 3 Recommendations</u>	<u>83</u>
<u>Appendix 8</u>	<u>BPI-SF (<i>sample only, not for patient use</i>).....</u>	<u>85</u>
<u>Appendix 9</u>	<u>EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>).....</u>	<u>88</u>
<u>Appendix 10</u>	<u>FACT-P (Functional Assessment of Cancer Therapy – Prostate) (<i>sample only, not for patient use</i>).....</u>	<u>92</u>
<u>Appendix 11</u>	<u>PCCTC Bone Scan Assessment Tool.....</u>	<u>96</u>

List of tables

<u>Table 1</u>	<u>Toxicity management and dose modification recommendations.....</u>	<u>38</u>
<u>Table 2</u>	<u>Screening procedures and baseline assessments</u>	<u>42</u>
<u>Table 3</u>	<u>Schedule of assessments: ^{177}Lu PSMA 617 plus best supportive/best standard of care arm (Cycle 1).....</u>	<u>71</u>
<u>Table 4</u>	<u>Schedule of assessments: ^{177}Lu PSMA 617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....</u>	<u>72</u>
<u>Table 5</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	<u>74</u>
<u>Table 6</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	<u>75</u>
<u>Table 1</u>	<u>Toxicity management and dose modification recommendations.....</u>	<u>38</u>

Page 11 of 101

<u>Table 2</u>	<u>Screening procedures and baseline assessments</u>	<u>42</u>
<u>Table 3</u>	<u>Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1).....</u>	<u>71</u>
<u>Table 4</u>	<u>Schedule of assessments: ^{177}Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....</u>	<u>72</u>
<u>Table 5</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)</u>	<u>74</u>
<u>Table 6</u>	<u>Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....</u>	<u>75</u>

List of figures

<u>Figure 1</u>	<u>Diagram of trial design</u>	<u>28</u>
<u>Figure 1</u>	<u>Diagram of trial design</u>	<u>28</u>

Page 12 of 101

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment: AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment: AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added.• Updated reference section
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01-April_08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 13 of 101

- since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.
- Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.
 - Additional imaging analyses details were added for study ⁶⁸Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.
 - Further clarification on the start and end timing for ⁶⁸Ga-PSMA-11 TEAEs, ¹⁷⁷Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
 - Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression.

Page 14 of 101

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare the two alternate primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p><u>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</u></p> <p><u>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up.</u></p> <p>A long-term follow-up period will include the collection of rPFS survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (\pm1 month) via phone, email, or letter for up to 24 months or until 489508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status</p>

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 15 of 101

	<p>updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).</p> <p>These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or <u>the date of the best supportive/best standard of care end of treatment decision</u> (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is <u>750814</u> patients.</p>
Study population:	<p>The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.</p>
Investigational product:	<p>Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ¹⁷⁷Lu-PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.</p>
Assessment schedule:	<p>Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit.</p> <p>The previous 2 PSA values will be noted before randomization. Serum/plasma testosterone and PSA levels will be measured up to 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (up to 3 days prior to each time point) and up to 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 12 weeks (± 4 days) until the patient starts long term follow up.</p> <p>Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.</p>
Statistical methodology:	<p><u>There will be 1Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis at the time of 457 rPFS events wherewill focus on patients randomized on or after March 5th, 2019; rPFS and OS will be evaluated for efficacy, followed bywill be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those</u></p>

Page 16 of 101

	<p>randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final analysis of OS will be performed when 489 OS events have occurred. 508 deaths have accrued and the alpha level applied will be 0.02 1-sided. This trial has at least 91.590% overall power and an overall Type I error rate of at most 0.025 1-sided.</p>
Duration of Study:	Total duration of the study will be approximately 38 months.

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April, 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 17 of 101

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQoL) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat

Page 18 of 101

Abbreviation	Term/Definition
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

Page 19 of 101

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral

Page 20 of 101

disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 4% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#), [Cheng et al 2015](#), [Badrising et al 2014](#), [Brasso et al 2015](#), [Loriot et al 2013](#), [Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#), [Ghosh and Heston 2004](#), [Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al 2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

Page 21 of 101

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium- β^- - emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β^- range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kulkarni et al 2018).

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research*. 2018 Jul;78(13):CT015.

Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Page 22 of 101

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ¹⁷⁷Lu-PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ¹⁷⁷Lu-PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in the prospective study xerostomia appears low grade and occurs at a rate of approximately 87% in treated patients. Clearance of ¹⁷⁷Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively.

The first published clinical series of ¹⁷⁷Lu-PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ¹⁷⁷Lu-PSMA-617 in 50 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018, Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ¹⁷⁷Lu-PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective response rate in measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ¹⁷⁷Lu-PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ¹⁷⁷Lu-PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ¹⁷⁷Lu-PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common

Page 23 of 101

side effects, predominately Grade 1-2, of ¹⁷⁷Lu-PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of

Page 24 of 101

approximately 16-27-fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Fendler et al 2017).

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly, and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Page 25 of 101

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Alternate Primary endpoints

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate

Page 26 of 101

Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. -Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, ~~or~~ requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy

Page 27 of 101

- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
- c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

- a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

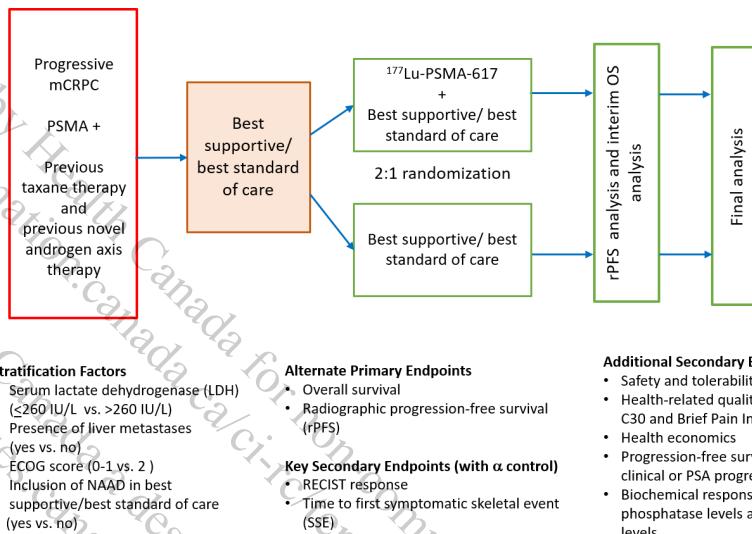


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and

Page 29 of 101

- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue ~~the randomized~~ treatment part of the study at any time. If a patient withdraws consent for the chooses only to discontinue from the ~~randomized~~ treatment part ~~or in the study for a reason other than radiographic progression~~, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw ~~for the consent from~~ long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues ~~the randomized~~ treatment part of ~~the study~~ for any reason (patient or investigator decision, going on to long term follow up, etc.).

~~This~~The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or ~~the date of the~~ best supportive/best standard of care ~~end of treatment decision~~ (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

~~If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.~~

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of ~~rPFS (if discontinuing for reasons other than radiographic progression)~~, survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing.

During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (± 1 month) via phone, email, or letter for up to 24 months or until ~~489508~~ deaths have occurred.

Patients who withdraw their consent to participate in ~~the treatment portion of the study or come off the treatment portion of~~ the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact

Page 30 of 101

person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 750 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Page 31 of 101

Reading of the baseline ^{68}Ga -PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “ ^{68}Ga -PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ^{68}Ga -PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ^{177}Lu -PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ^{177}Lu -PSMA-617 at time of injection.

Refer to the ^{177}Lu -PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu -PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu -PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu -PSMA-617 is well tolerated according to the clinical experience that has been documented in 42 publications, summarizing the safety and or efficacy information from over 800 subjects. Across these studies doses have ranged from 1.1-12.0 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-9 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However, efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Page 32 of 101

Clinical series now show reports of more than 4 cycles of ¹⁷⁷Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018, Kulkarni et al 2018, Bräuer et al 2017, Yordanova et al 2017). In addition, a recent review suggests optimal dosing of 6 cycles of ¹⁷⁷Lu-PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ¹⁷⁷Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ¹⁷⁷Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ¹⁷⁷Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

Page 33 of 101

~~Total duration of It is anticipated that it will take approx. 14 months to randomize the trial for required 814 patients in the study. After the last patient is randomized patients, considering expected survival, is expected to be 19 to 23 months, including a 1 month screening period, 6 to 10 month treatment period and a long term follow up period for safety and survival lasting will be followed for up to 24 months or at least until 489508 deaths have occurred. TotalThe maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.~~

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until ~~489508~~ deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND WITHDRAWAL DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. ~~ParticipantsWhile full follow-up is intended in the ITT population for the planned duration of the trial, participants~~ must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must be ^{68}Ga -PSMA-11 PET/CT scan positive, and eligible as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 34 of 101

9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation, intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum/plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, [Scher et al 2016](#)).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
 - a. Bone marrow reserve:
 - White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
 - Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
 - Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)
 - b. Hepatic:
 - Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

Page 35 of 101

c. Renal:

- Serum/plasma creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min

15. Albumin > 3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)

[Inclusion #16 has been removed]

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 6 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:

- Are allowed by the protocol
- Have been agreed to by the treating investigator and patient
- Allow for the management of the patient without ^{177}Lu -PSMA-617

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization:
Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).

Page 36 of 101

8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only withdraws consent for to discontinue from the randomized treatment part efin the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is intent to treatITT so that all subjects willare to be followed for up to 24 months for safety and survival or until 489508 deaths have occurred. -The total of 489508 deaths are expected to have occurred approximately +513 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ⁶⁸Ga-PSMA-11

For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure. The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

Page 37 of 101

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(\pm 5) minutes before and at 30(\pm 5) and 60(\pm 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Page 38 of 101

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count $<3.0 \times 10^9/\text{L}$• ANC $<1.5 \times 10^9/\text{L}$	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of $< 75 \times 10^9/\text{L}$)	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Transfusions may be given as clinically indicated for thrombocytopenia.
Hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle
Serum/plasma creatinine increased $\geq 40\%$ from baseline AND calculated creatinine clearance decreased $>40\%$ from baseline		Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (not amenable to medical intervention)	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 12 weeks.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

Page 40 of 101

The best supportive/best standard of care for the patient in either arm should be administered as per physician's orders and protocol at the institution, and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating

Page 41 of 101

factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g., radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

If a patient discontinues the treatment part of the study for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any

Page 42 of 101

medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum/plasma testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks (+ 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. Study eligibility based on PSMA positivity will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT= computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, Scher et al 2016). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ⁶⁸Ga-PSMA-11 scan data will be used for additional exploratory analyses. The ⁶⁸Ga-PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ⁶⁸Ga-PSMA-11 PET/CT scans by assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ⁶⁸Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ⁶⁸Ga-PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.26.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see Appendix 6 and Appendix 7).

6.2.36.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirements for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

6.2.46.2.5 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

Page 45 of 101

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.56.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993, Esper et al 1997](#))
- Available in over 45 different languages

Page 46 of 101

- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.66.2.7 Health Economics

A health economics (HE) sub-study will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.76.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.86.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum/plasma testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry

*total carbon dioxide or equivalent is acceptable

- Sodium
- potassium
- total and direct bilirubin
- ALP
- AST
- ALT
- urine pH
- protein content
- specific gravity
- appearance and color

Urinalysis

** urea is acceptable

- LDH
- blood urea nitrogen**
- creatinine
- uric acid
- phosphorus
- chloride
- glucose
- ketones

Hematology

- complete blood count (white blood cell count and differential)
- red blood cell count
- hemoglobin
- hematocrit
- platelet count

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control ([e.g.](#), condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 6 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

Page 48 of 101

6.5 Long-term follow-up procedures

A long-term follow-up period will collect self reported, long term follow-up specific self-reported AE assessments, and PFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company
01 April 08

Page 49 of 101

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Progression of disease is not considered an AE or SAE for this study.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended response to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death; except for deaths due to progression of disease• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event.

7.2 Evaluating and recording adverse events

All adverse events (AEs) will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the last dose or intervention identified as date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the

Page 50 of 101

AE was caused by ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is “unknown and of questionable relationship to the study drug” the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is “unknown but not related to the study drug” the determination and rationale will be documented in the patient’s case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study. ~~If, after the study has begun,~~

~~All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as important subgroups, will be described.~~

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). ~~Changes~~Any changes to exploratory or

Page 52 of 101

non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Post|Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the Statistical Analysis Plan (SAP). Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

~~All statistical analyses will be carried out using SAS version 9.3 (or later). The SAP will be written and finalized prior to the first planned analysis and without knowledge of any by treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.~~

8.18.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 750814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 4314 months, a total of 750814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield (i) 457 rPFS events and 249508 deaths with a minimum follow up of 3-4 months after the last patient is. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized and (ii) 489 death on or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events with a minimum follow up of 15 months after the last patient is which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is or 0.67 or better with a 1-sided alpha level if 0.004. At the time of this rPFS analysis, 341 deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The analyses of rPFS and OS are event driven. The analysis of rPFS is planned with 457 events with an allocated 1-sided alpha level of 0.001. An interim analysis of OS is planned to coincide with this analysis of rPFS at which time 249 deaths are expected; the allocated 1-sided alpha level for OS at the interim will be 0.001. A final analysis of OS will take place with 489 deaths which are expected to have accrued with 15 months follow up post the last patient randomized.

Page 53 of 101

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if both achieve p<0.004 1-sided is achieved for rPFS and p<0.001 1-sided, then the alpha level for the final analysis of OS will be raised to 0.025-1-sided.
- if only one reaches p<0.004 1-sided is achieved for rPFS but p<0.001 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if neither reaches p<0.004 1-sided is not achieved for rPFS but p<0.001 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.023021 1-sided.
- if p<0.004 1-sided is not achieved for rPFS and p<0.001 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; overall power is at least 91.4% and the overall Type I error rate is ≤0.025 1-sided.

The observed HRs that will meet $p<0.001004$ for rPFS and the interim analysis of OS are 0.736745 and 0.660701 respectively; and the observed HR that will meet $p<0.023020$ to $p<0.025$ in the final analysis of OS are 0.826824 to 0.829823.

8.28.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. Patient efficacy data in this dataset OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.38.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard

Page 54 of 101

deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.48.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.58.7 Efficacy analyses

8.5.18.7.1 Alternate primary endpoint efficacy analysis

8.5.1.18.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. The primary analysis of rPFS is event driven will be based upon the PFS-FAS and will take place once 457364 rPFS events have been reached. -The allocated alpha level for the rPFS analysis is 0.001004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified Cox proportional hazards regression log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset. The model will include a single covariate for randomized treatment and will be stratified for the randomization stratification factors. The HR (active: control), its 95% confidence interval, and the associated 1-sided p value will be presented. A supportive analysis will be provided via..

Supportive analyses of rPFS will be performed in terms of (i) a stratified log rank test, Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.5.1.28.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause—and will be assessed in the FAS. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 457364 rPFS events in PFS-FAS); it is anticipated that approximately 249341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. -The final analysis of OS is event driven and will take place once 489508 deaths have occurred—in the FAS. As described in Section 8.43, the allocated alpha level for the final OS analysis will be between 0.023020 and 0.0251025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed in the same manner as rPFS. OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.5.1.38.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS or OS at the respective allocated alpha level; it is not required to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level or OS to meet its allocated alpha level at either (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) or (ii) at the final OS analysis with 489508 deaths.

Alpha allocation and recycling is are used to ensure control of the overall Type I error rate as described in Section 8.43.

8.5.28.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

Page 56 of 101

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model in the same manner as described with a single covariate for randomized treatment, stratifying for the alternate primary endpoints. Objective response and randomization stratification factors, ORR and disease control rate DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ^{177}Lu -PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS isas defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for the alternate primary endpoint time to SSE except using a 2-sided p-value. Disease control rate DCR will be analyzed in the same manner as objective response rate ORR and HRQoL will be analyzed in the same manner as pain score over

Page 57 of 101

time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.6.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set.

8.6.18.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.6.28.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ⁶⁸Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ⁶⁸Ga-PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ⁶⁸Ga-PSMA-11 dosing up to 6 days after the date of ⁶⁸Ga-PSMA-11 dosing as long as prior to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ⁶⁸Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ⁶⁸Ga-PSMA-11 TEAEs. Unrelated ⁶⁸Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.6.38.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

Page 58 of 101

8.6.48.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.78.9 IDMC and Interim Data Evaluation

8.718.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. -Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. -The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 457364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 489508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.7.28.9.2 Formal Interim Analysis of OS

As described above in Section 8.1.8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis. in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 489508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible

Page 59 of 101

government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

Page 60 of 101

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte

Page 61 of 101

will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 62 of 101

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company
01 April 08

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ^{177}Lu -PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ^{177}Lu -DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015, 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bräuer et al 2017

Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ^{177}Lu -PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017 Sep;44(10):1663-70.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Page 64 of 101

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

Page 65 of 101

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ¹⁷⁷Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [¹⁷⁷Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Page 66 of 101

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Clin Oncol. 2019;37(suppl 7S): 228.

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research. 2018 Jul;78(13):CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987-88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807-1812. doi:10.1093/annonc/mdt136

Page 67 of 101

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With ^{177}Lu -PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of ^{177}Lu -PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating ^{177}Lu -PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flehsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print]

Page 68 of 101

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 69 of 101

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ^{177}Lu -DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using $[^{177}\text{Lu}]\text{Lu-PSMA-617}$ on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017;DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 70 of 101

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

Endocyte, Inc., a Novartis Company
01 April 08

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^a	X					X
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum/plasma testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(\pm 5) minutes before, 30 (\pm 5) minutes post, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X						X ^a	X	
AE monitoring ^b	X						X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/ best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	
Serum/plasma testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

Protocol no. PSMA-617-01
Version no.: 34.0

Endocyte, Inc., a Novartis Company
01-April-08 July 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- * After the Cycle 4 dose of ¹⁷⁷Lu-PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
 - The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
 - Has signs of residual disease on CT with contrast/MRI or bone scan and
 - has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.
- If the patient meets the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.
- ** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.
- a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
- b Adverse event monitoring will commence at time of consent.
- c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30(+/-5) minutes post, and 60(+/-5) minutes post ¹⁷⁷Lu-PSMA-617 administration.
- e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (\pm 4 days).
- g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study
- h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA= prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum/plasma testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after Cycle 1 Day 1 ^g for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will commence at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (\pm 4 days)		Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X ^a						X ^a	X	
AE monitoring ^b	X						X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^b	X	
Serum/plasma testosterone	X ^c						X ^b	X	
PSA	X ^c						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after Cycle 1 Day 1 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)								

** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

Page 76 of 101

- a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
- b Adverse event monitoring will commence at time of consent.
- c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
- e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- f For Cycles 2 to 6; Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).
- g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
- h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Protocol no. PSMA-617-01
Version no. 34.0

Endocyte, Inc., a Novartis Company
01 April 08 July 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 77 of 101

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ¹⁷⁷Lu-PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ¹⁷⁷Lu-PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ¹⁷⁷Lu-PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ¹⁷⁷Lu-PSMA-617 therapy

Protocol no. PSMA-617-01
Version no.: 34.0
July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company
01 April, 08

Page 78 of 101

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Page 79 of 101

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Page 80 of 101

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 81 of 101

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Page 82 of 101

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Record outcome as new lesions, no new lesions or resolved lesion• First scheduled reassessment:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ New lesions: perform a confirmatory scan 6 or more weeks later• Confirmatory scan:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ Additional new lesions: progression• Subsequent scheduled reassessments:<ul style="list-style-type: none">◦ No new lesions: continue◦ New lesions: progression• Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">• Exclude pseudoprogression in the absence of symptoms or other signs of progression• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented• For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan• Date of progression is the date of the scan that first documents the second lesion• Changes in intensity of uptake alone do not constitute either progression or regression• Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve end points:</p> <ul style="list-style-type: none">• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 85 of 101

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 86 of 101

Brief Pain Inventory (Short Form)

Time: ____ : ____ AM PM
Today's Date (day, month, year):

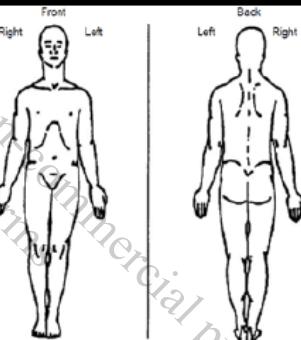
Today's Date (day, month, year).
JAN JAN MAR MAR MAY MAY JUL JUL SEP SEP NOV NOV
FEB FEB APR APR JUN JUN AUG AUG OCT OCT DEC DEC

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.



4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.



5. Please rate your pain by circling the one number that best describes your pain on the average.



6. Please rate your pain by circling the one number that best describes how much pain you have right now.



Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 87 of 101

Today's Date (Day, Month, Year): _____ (Example: 08-FEB-2016) DAY MONTH YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 88 of 101

**Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5
Level scale) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 89 of 101



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 90 of 101

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

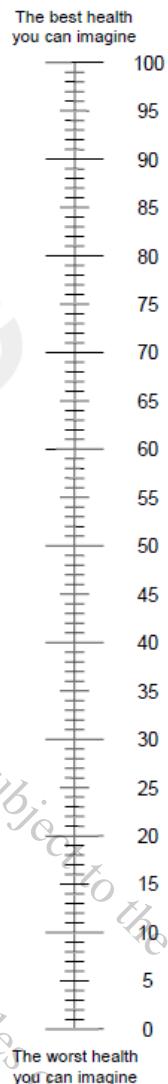
ANXIETY / DEPRESSION

- I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

Page 91 of 101

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 92 of 101

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy –
Prostate) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

Page 95 of 101

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNs</u>	Not at all	A little bit	Somewhat	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

19 November 2007
Page 3 of 3

Page 96 of 101

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

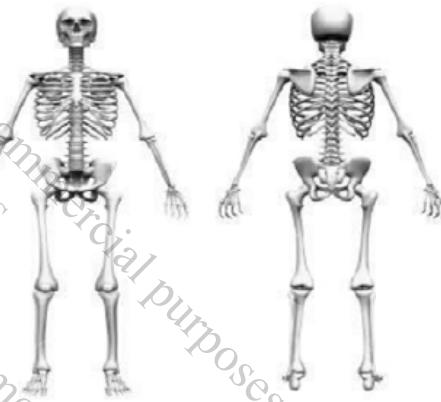
Page 97 of 101

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

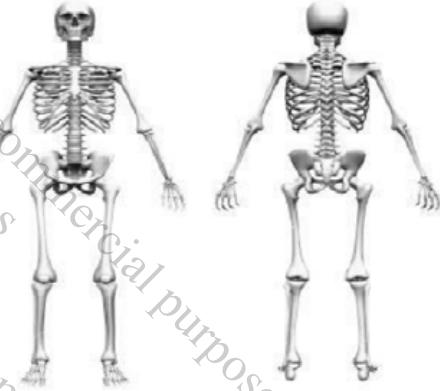
Page 98 of 101

Week 8 BASELINE Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input checked="" type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ? <input type="checkbox"/> Yes* <input type="checkbox"/> No	
* Presence of new lesions at this time does not confirm progression	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

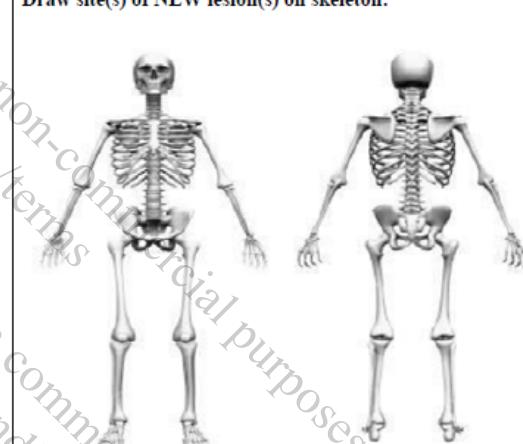
Page 99 of 101

Week 16 Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m} Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

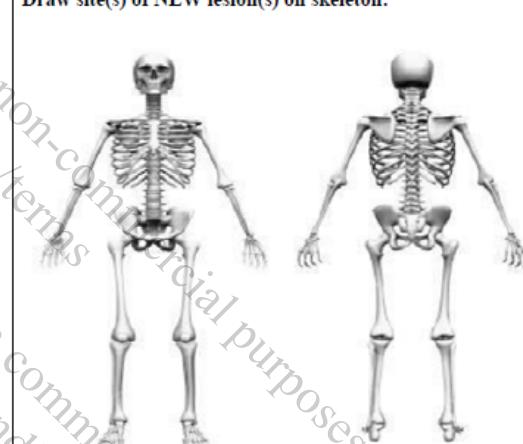
Page 100 of 101

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date:	<u>D D - M M M - Y Y Y</u>
Is there radiolabeled tracer (e.g., ^{99m} Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 101 of 101

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date:	<u>D D - M M M - Y Y Y</u>
Is there radiolabeled tracer (e.g., ^{99m} Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

""

Signature Manifest

Document Number: TMF-02-0003

Revision: 04

Title: 2.1.4 Protocol Amendment

All dates and times are in US/Eastern.

2.1.4 VISION 4.0

Clinical Review

Name/Signature	Title	Date	Meaning/Reason	
PI	PI	INFOSYS	09 Jul 2019, 11:04:21 AM	Complete

Clinical Approval

Name/Signature	Title	Date	Meaning/Reason
PI	PI	09 Jul 2019, 11:21:47 AM	Approved
Rich Messmann (RMESSMANN)	VP, Medical Affairs	09 Jul 2019, 12:09:41 PM	Approved
PI	PI	09 Jul 2019, 12:35:56 PM	Approved
		09 Jul 2019, 02:25:41 PM	Approved
		09 Jul 2019, 04:43:24 PM	Approved

Printed on: ; Printed by: .

""



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER,
RANDOMIZED PHASE 3 STUDY OF ^{177}Lu -PSMA-617 IN THE TREATMENT OF
PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-
RESISTANT PROSTATE CANCER (MCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 4.0

Date: 08 July 2019

IND No.: 133,661 (^{177}Lu -PSMA-617)
133,925 or site equivalent (^{68}Ga -PSMA-11)

EudraCT No. 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ^{177}Lu -PSMA-617; ^{68}Ga -PSMA-11

Sponsor: Endocyte, Inc., A Novartis Company
3000 Kent Avenue, Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Printed on: ; Printed by: .

Page 2 of 95

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Page 3 of 95

Table of Contents

Site Principal Investigator Signature.....	2
Table of Contents.....	3
Revision History	7
Clinical Trial Summary.....	9
List of Abbreviations and Definitions.....	12
1. Introduction	14
1.1 Background information.....	14
1.2 Summary of nonclinical studies with clinical significance	18
1.3 Summary of known and potential risks and benefits	19
2. Trial Objectives and Endpoints	19
2.1 Trial objectives.....	19
2.1.1 Primary objective.....	19
2.1.2 Key secondary objectives	20
2.1.3 Additional secondary objectives.....	20
2.2 Trial endpoints	20
2.2.1 Alternate Primary endpoints.....	20
2.2.2 Key Secondary endpoints	20
2.2.3 Additional Secondary endpoints.....	21
3. Trial Design.....	22
3.1 Overview of the clinical trial design.....	22
3.1.1 Study design update	24
3.2 Rationale for the study design	25
3.3 Measures taken to minimize/avoid bias	25
3.4 Description of the clinical trial	25
3.4.1 Description of investigational medicinal product.....	25
3.4.2 Dosage and rationale for dose selection	25
3.4.3 Subject allocation to treatment	26
3.4.4 End of treatment visit	27
3.4.5 Duration of Subject Participation.....	27
3.5 End of trial definition	27
4. Selection andDISCONTINUATION of Subjects.....	27
4.1 Inclusion criteria	27
4.2 Exclusion criteria	29
4.3 Subject withdrawal of consent for study or treatment	30
5. Treatment of Subjects	31
5.1 Treatment with the investigational medicinal product.....	31

Page 4 of 95

5.1.1	Administration of ⁶⁸ Ga-PSMA-11	31
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-617	31
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	31
5.1.4	Management of toxicity adverse events: dosing delays and modification.....	32
5.2	Best supportive/best standard of care.....	34
5.3	Concomitant medications/ supportive care.....	35
5.3.1	Permitted concomitant medications/ supportive care	35
5.3.2	Prohibited concomitant medications	35
5.4	Monitoring treatment compliance.....	35
5.5	Treatment discontinuation	35
6.	Study Assessments and Procedures	36
6.1	Screening procedures and baseline assessments.....	36
6.2	Efficacy assessments	38
6.2.1	Radiographic imaging for tumor assessments	38
6.2.2	Additional Imaging Analyses	38
6.2.3	RECIST criteria	39
6.2.4	Symptomatic skeletal events	39
6.2.5	Pain score.....	39
6.2.6	Health-related quality of life.....	39
6.2.7	Health Economics	40
6.2.8	Clinical progression	40
6.2.9	PSA levels	41
6.3	Safety assessments	41
6.3.1	Clinical laboratory evaluations	41
6.3.2	Vital signs	41
6.3.3	Electrocardiograms	41
6.3.4	Birth Control.....	41
6.4	End of treatment visit procedures	41
6.5	Long-term follow-up procedures	42
7.	Adverse Events	42
7.1	Adverse event definitions	42
7.2	Evaluating and recording adverse events	43
7.3	Immediate Adverse Event Reporting	44
7.3.1	Serious Adverse Events.....	44
7.3.2	Serious adverse event subject follow-up.....	44
7.3.3	Sponsor Contact Information for Immediate Reporting	44
8.	Statistics	45

Page 5 of 95

8.1	Revision to the protocol and statistical analyses of rPFS and OS	45
8.2	Revisions to planned analyses	45
8.3	Sample size and power determination.....	46
8.4	Analysis populations	47
8.5	Demographics and baseline disease characteristics	47
8.6	Patient disposition	47
8.7	Efficacy analyses.....	47
8.7.1	Alternate primary endpoint efficacy analysis	47
8.7.2	Secondary efficacy analyses	49
8.8	Safety analyses.....	50
8.8.1	Extent of exposure	50
8.8.2	Analysis of adverse events	50
8.8.3	Analysis of laboratory assessments.....	51
8.8.4	Analysis of vital sign data	51
8.9	IDMC and Interim Data Evaluation.....	51
8.9.1	IDMC	51
8.9.2	Formal Interim Analysis of OS.....	51
9.	Access to Source Data/Documents	52
10.	Ethics.....	52
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB).....	52
10.2	Informed consent.....	52
10.3	Health Insurance Portability and Accountability Act	53
10.4	Confidentiality	53
11.	Compliance and quality control.....	53
11.1	Compliance with Monitoring and Audits	53
12.	Data Handling, Record Keeping, and Compliance	54
12.1	Investigational medicinal product accountability	54
12.2	Breaking the blind	54
12.3	Data collection forms and source document identification	54
12.4	Record maintenance and retention	55
12.5	Archiving	55
13.	Publication Policy	55
14.	References	57
Appendix 1	Schedules of Assessments.....	64
Appendix 2	Suggested treatment guidelines	71
Appendix 3	Principal Investigator Signature	72

Appendix 4a	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	73
Appendix 4b	Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	74
Appendix 5	Common Terminology Criteria for Adverse Events	75
Appendix 6	Response Evaluation Criteria in Solid Tumors.....	76
Appendix 7	Prostate Cancer Working Group 3 Recommendations.....	77
Appendix 8	BPI-SF (<i>sample only, not for patient use</i>)	79
Appendix 9	EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	82
Appendix 10	FACT-P (Functional Assessment of Cancer Therapy – Prostate) (<i>sample only, not for patient use</i>).....	86
Appendix 11	PCCTC Bone Scan Assessment Tool.....	90

List of tables

Table 1	Toxicity management and dose modification recommendations	32
Table 2	Screening procedures and baseline assessments.....	36
Table 3	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1).....	65
Table 4	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....	66
Table 5	Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)	68
Table 6	Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU).....	69

List of figures

Figure 1	Diagram of trial design.....	22
----------	------------------------------	----

Page 7 of 95

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment: AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment: AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added.• Updated reference section
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.

Page 8 of 95

		<ul style="list-style-type: none">Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.Additional imaging analyses details were added for study ⁶⁸Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.Further clarification on the start and end timing for ⁶⁸Ga-PSMA-11 TEAEs, ¹⁷⁷Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression,
--	--	--

Page 9 of 95

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare the two alternate primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory - Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</p> <p>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up.</p> <p>A long-term follow-up period will include the collection of rPFS survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (\pm1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which</p>

Page 10 of 95

	<p>may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).</p> <p>These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 814 patients.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ¹⁷⁷ Lu-PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ¹⁷⁷ Lu-PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ¹⁷⁷ Lu-PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ¹⁷⁷ Lu-PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷ Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷ Lu-PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum/plasma testosterone and PSA levels will be measured up to 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (up to 3 days prior to each time point) and up to 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 12 weeks (± 4 days) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Statistical methodology:	Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5 th , 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5 th , 2019). Following the analysis of rPFS and the interim analysis of OS, a final

Page 11 of 95

	analysis of OS will be performed when 508 deaths have accrued and the alpha level applied will be 0.02 1-sided. This trial has at least 90% overall power and an overall Type I error rate of at most 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

Page 12 of 95

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BPI-SF	Brief Pain Inventory – Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DOOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQoL) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous

Page 13 of 95

Abbreviation	Term/Definition
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

Page 14 of 95

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease ([Ferlay et al 2013](#), [Bray et al 2012](#)).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men ([Siegel et al 2017](#)), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months ([Smith et al 2016](#)). Post-docetaxel mCRPC patients have an annual death rate of 73% ([Scher et al 2015](#)).

The median age at diagnosis of mCRPC is 70 years ([Flaig et al 2016](#)). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases ([Kirby et al 2011](#)), and 49% of them will develop a serious skeletal event within 2 years ([Saad et al 2004](#)). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being ([Weinfurt et al 2005](#)). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved

Page 15 of 95

agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 4% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#), [Cheng et al 2015](#), [Badrising et al 2014](#), [Brasso et al 2015](#), [Loriot et al 2013](#), [Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#), [Ghosh and Heston 2004](#), [Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al 2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity

Page 16 of 95

ligand to PSMA, such as the targeting moiety in ¹⁷⁷Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

¹⁷⁷Lu-PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ¹⁷⁷Lu-PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ¹⁷⁷Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer and can be radiolabeled with gallium-68 (⁶⁸Ga), lutetium-177 (¹⁷⁷Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (⁹⁰Y).

¹⁷⁷Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ¹⁷⁷Lu is a medium- β^- - energy β^- - emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β^- range of ¹⁷⁷Lu provides better irradiation of small tumors, in contrast to the longer β -range of ⁹⁰Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ¹⁷⁷Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ¹⁷⁷Lu-PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ¹⁷⁷Lu to prostate cancer cells.

¹⁷⁷Lu-PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ¹⁷⁷Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kulkarni et al 2018).

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research*. 2018 Jul;78(13):CT015.

Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ¹⁷⁷Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where

Page 17 of 95

expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in the prospective study xerostomia appears low grade and occurs at a rate of approximately 87% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥ 6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 50 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018](#), [Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective response rate in measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ^{177}Lu -PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1–2, of ^{177}Lu -PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The

Page 18 of 95

incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27-fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the

Page 19 of 95

proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC

(Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Fendler et al 2017)

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly, and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 67% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Page 20 of 95

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

2.2 Trial endpoints

2.2.1 Alternate Primary endpoints

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

Page 21 of 95

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy

Page 22 of 95

- Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
- c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

- a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone ([Figure 1](#)).

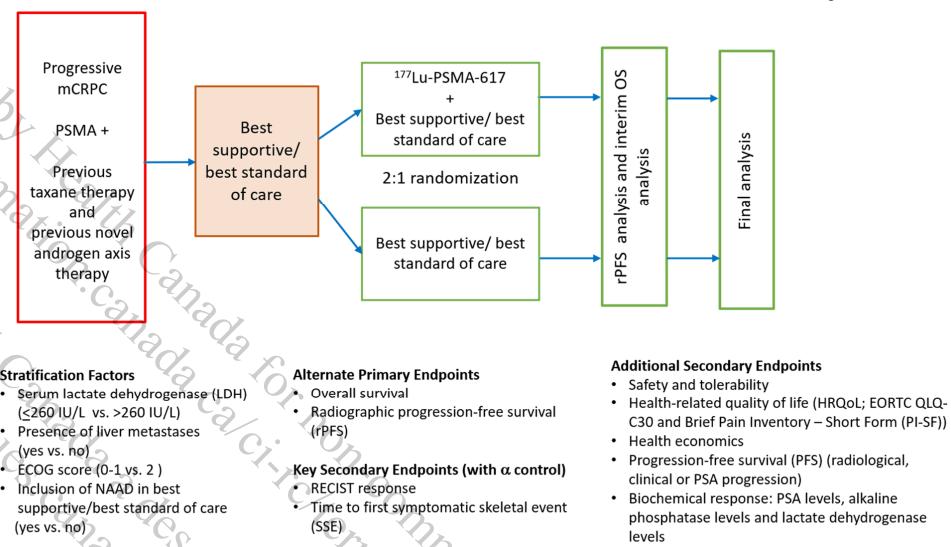


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and

Page 24 of 95

- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (± 1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact

Page 25 of 95

person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Page 26 of 95

Reading of the baseline ^{68}Ga -PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “ ^{68}Ga -PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ^{68}Ga -PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ^{177}Lu -PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ^{177}Lu -PSMA-617 at time of injection.

Refer to the ^{177}Lu -PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu -PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu -PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu -PSMA-617 is well tolerated according to the clinical experience that has been documented in 42 publications, summarizing the safety and or efficacy information from over 800 subjects. Across these studies doses have ranged from 1.1-12.0 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-9 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However, efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Page 27 of 95

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018, Kulkarni et al 2018, Bräuer et al 2017, Yordanova et al 2017). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu -PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu -PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu -PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu -PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm (^{177}Lu -PSMA-617 plus best supportive/best standard of care) or the best supportive/best standard of care-only arm using a permuted block scheme. Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

Page 28 of 95

It is anticipated that it will take approx. 14 months to randomize the required 814 patients in the study. After the last patient is randomized patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to [Section 8.1](#).

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must be ^{68}Ga -PSMA-11 PET/CT scan positive, and eligible as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).

Page 29 of 95

10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g. frailty assessed by geriatric or health status evaluation, intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum/plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
 - a. Bone marrow reserve:
 - White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/cumm$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/cumm$ and $1500/\mu L$)
 - Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/cumm$ and $100,000/\mu L$)
 - Hemoglobin ≥ 9 g/dL (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)
 - b. Hepatic:
 - Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases
 - c. Renal:
 - Serum/plasma creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min

Page 30 of 95

15. Albumin >3.0 g/dL (3.0 g/dL is equivalent to 30 g/L)
[Inclusion #16 has been removed]
17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.
18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 6 months after last study drug administration.
19. The best standard of care/ best supportive care options planned for this patient:
 - a. Are allowed by the protocol
 - b. Have been agreed to by the treating investigator and patient
 - c. Allow for the management of the patient without ¹⁷⁷Lu-PSMA-617

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.

Page 31 of 95

10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga -PSMA-11

For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure. The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

Refer to the Fendler et al 2017 publication “ ^{68}Ga -PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ^{68}Ga -PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

Page 32 of 95

A saline flush with ≥ 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(+/- 5) minutes before and at 30(+/- 5) and 60(+/- 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results

must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. **Table 1** provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count $<3.0 \times 10^9/\text{L}$• ANC $<1.5 \times 10^9/\text{L}$	$\geq\text{Grade } 2$	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematinic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of $<75 \times 10^9/\text{L}$)	$\geq\text{Grade } 2$	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Transfusions may be given as clinically indicated for thrombocytopenia.
Hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle
Serum/plasma creatinine increased $\geq 40\%$ from baseline AND calculated creatinine clearance decreased $>40\%$ from baseline		Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	$\geq\text{Grade } 2$	Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	$\geq\text{Grade } 2$	Hold ^{177}Lu -PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	$\geq\text{Grade } 2$	Hold ^{177}Lu -PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (not amenable to medical intervention)	$\geq\text{Grade } 3$	Hold ^{177}Lu -PSMA-617 administration until resolved to Grade 2 or baseline Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Fatigue	≥ Grade 3	Hold ^{177}Lu -PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ^{177}Lu -PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ^{177}Lu -PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ^{177}Lu -PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT $>5 \times \text{ULN}$ in the absence of liver metastases		Discontinue ^{177}Lu -PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ^{177}Lu -PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ^{177}Lu -PSMA-617
Any unacceptable toxicity		Discontinue ^{177}Lu -PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 12 weeks.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm should be administered as per physician's orders and protocol at the institution, and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Page 35 of 95

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchiectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section [5.1.4](#) for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g., radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ^{177}Lu -PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

If a patient discontinues the treatment part of the study for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
	<ul style="list-style-type: none">• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum/plasma testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks (+ 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. Study eligibility based on PSMA positivity will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria).

Page 39 of 95

If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ^{68}Ga -PSMA-11 scan data will be used for additional exploratory analyses. The ^{68}Ga -PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ^{68}Ga -PSMA-11 PET/CT scans by assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ^{68}Ga -PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ^{68}Ga -PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

6.2.5 Pain score

Pain will be assessed using the Brief Pain Inventory – Short Form (BPI-SF).

The Brief Pain Inventory- Short Form will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)).

Page 40 of 95

This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993](#), [Esper et al 1997](#))
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) sub-study will be performed.. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in

Page 41 of 95

terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum/plasma testosterone, and urinalysis testing.

Page 42 of 95

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry

*total carbon dioxide or equivalent is acceptable

** urea is acceptable

- Sodium
- potassium
- total and direct bilirubin
- ALP
- AST
- ALT

- LDH
- blood urea nitrogen**
- creatinine
- uric acid
- phosphorus
- chloride
- glucose
- ketones

- bicarbonate*
- calcium
- glucose
- total protein
- albumin

Urinalysis

- urine pH
- protein content
- specific gravity
- appearance and color

Hematology

- complete blood count (white blood cell count and differential)
- red blood cell count
- hemoglobin
- hematocrit
- platelet count

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g., condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 6 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect, long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission

Page 43 of 95

to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Progression of disease is not considered an AE or SAE for this study.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended response to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death; except for deaths due to progression of disease• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

Page 44 of 95

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11, ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

Page 45 of 95

SAEs which are: 1) associated with ^{68}Ga -PSMA-11, ^{177}Lu -PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis

Page 46 of 95

of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non- confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). |Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized on or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341 deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

Page 47 of 95

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p < 0.004$ 1-sided is achieved for rPFS and $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p < 0.004$ 1-sided is achieved for rPFS but $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS but $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS and $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p < 0.020$ to $p < 0.025$ in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint efficacy analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. The primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, stratified for the randomization stratification factors..

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final

Page 49 of 95

analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is **not required** to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level **or** OS to meet its allocated alpha level at **either** (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) **or** (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

Page 50 of 95

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ^{177}Lu -PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - d. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - e. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value. DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by Ellis et al 2008.

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set.

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga -PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga -PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ^{68}Ga -PSMA-11 dosing up to 6 days after the date of ^{68}Ga -PSMA-11 dosing as long as prior to the first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ^{68}Ga -PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ^{68}Ga -PSMA-11 TEAEs. Unrelated ^{68}Ga -PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and Interim Data Evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical

Page 52 of 95

analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal Interim Analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective

Page 53 of 95

IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

Page 54 of 95

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Page 55 of 95

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

Page 56 of 95

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015, 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bräuer et al 2017

Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ¹⁷⁷Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017 Sep;44(10):1663-70.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Page 58 of 95

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

Page 59 of 95

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with ¹⁷⁷Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [¹⁷⁷Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [¹⁷⁷Lu]-PSMA-

Page 60 of 95

617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. J Clin Oncol. 2019;37(suppl 7S): 228.

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. J Nucl Med. 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. Cancer Research. 2018 Jul;78(13):CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987-88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with ¹⁷⁷Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009 June;15(2):167–72.

Page 61 of 95

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013;24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With ^{177}Lu -PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of ^{177}Lu -PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfar J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating ^{177}Lu -PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfar H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXL Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnumed.117.194209. doi: 10.2967/jnumed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S414 EP482.

Page 62 of 95

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Page 63 of 95

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ^{177}Lu -DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging*. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using $[^{177}\text{Lu}]$ -PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2017;DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. *Can Urol Assoc J*. 2014 Jul;8(7-8):E520-3.

Page 64 of 95

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 4.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company
08 July 2019

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^a	X					X
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum/plasma testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(\pm 5) minutes before, 30 (\pm 5) minutes post, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no. 4.0

Endocyte, Inc., a Novartis Company
08 July 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X-----X ^a						X		
AE monitoring ^b	X-----X ^a						X		
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/ best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	
Serum/plasma testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

Protocol no. PSMA-617-01
Version no. 4.0

Endocyte, Inc., a Novartis Company
08 July 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- * After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
 - The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
 - Has signs of residual disease on CT with contrast/MRI or bone scan and
 - has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.
- If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone.
- ** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.
- a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
- b Adverse event monitoring will commence at time of consent.
- c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1) and at 15(+/-5) minutes before, 30(+/-5) minutes post, and 60(+/-5) minutes post ^{177}Lu -PSMA-617 administration.
- e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (\pm 4 days).
- g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study
- h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum/plasma testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after Cycle 1 Day 1 ^g for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will commence at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen

Protocol no. PSMA-617-01
Version no. 4.0

Endocyte, Inc., a Novartis Company
08 July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (\pm 4 days)		Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X ^a						X ^a	X	
AE monitoring ^b	X						X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^b	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^b	X	
Serum/plasma testosterone	X ^c						X ^b	X	
PSA	X ^c						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after Cycle 1 Day 1 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)								

^{**}Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

Page 70 of 95

- ^a Phone evaluations are allowed, but are not required for visits after Day 1 of each cycle.
- ^b Adverse event monitoring will commence at time of consent.
- ^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- ^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
- ^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- ^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).
- ^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
- ^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Protocol no. PSMA-617-01
Version no. 4.0

Endocyte, Inc., a Novartis Company
08 July 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ¹⁷⁷Lu-PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ¹⁷⁷Lu-PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ¹⁷⁷Lu-PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ¹⁷⁷Lu-PSMA-617 therapy

Page 72 of 95

Appendix 3 Principal Investigator Signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Page 73 of 95

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Page 74 of 95

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 75 of 95

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 76 of 95

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Page 78 of 95

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Record outcome as new lesions, no new lesions or resolved lesion• First scheduled reassessment:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ New lesions: perform a confirmatory scan 6 or more weeks later• Confirmatory scan:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ Additional new lesions: progression• Subsequent scheduled reassessments:<ul style="list-style-type: none">◦ No new lesions: continue◦ New lesions: progression• Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">• Exclude pseudoprogression in the absence of symptoms or other signs of progression• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented• For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan• Date of progression is the date of the scan that first documents the second lesion• Changes in intensity of uptake alone do not constitute either progression or regression• Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 79 of 95

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Brief Pain Inventory (Short Form)

Time: ____ : ____ AM PM
Today's Date (day, month, year):

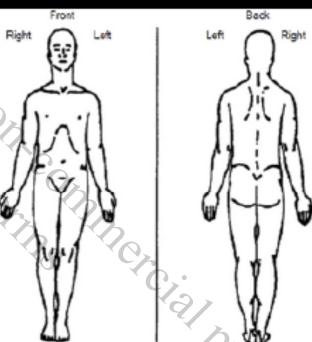
Day JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Page 81 of 95

Today's Date (Day, Month, Year): _____ (Example: 08-FEB-2016) DAY MONTH YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 82 of 95

**Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5
Level scale) (sample only, not for patient use)**

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 83 of 95



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

Page 84 of 95

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

-
-
-
-
-

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

-
-
-
-
-

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

-
-
-
-
-

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

-
-
-
-
-

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

-
-
-
-
-

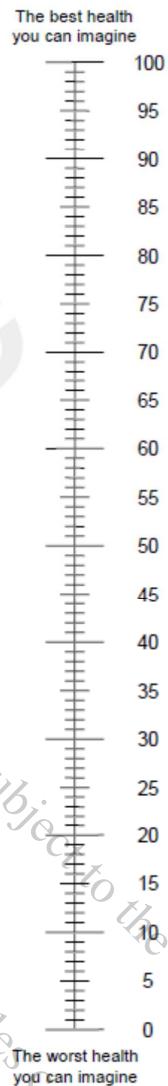
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 85 of 95

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 86 of 95

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy –
Prostate) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

Page 88 of 95

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad.....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home).....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

Page 89 of 95

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNs	Not at all	A little bit	Somewhat	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

19 November 2007
Page 3 of 3

Page 90 of 95

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01 April 2019

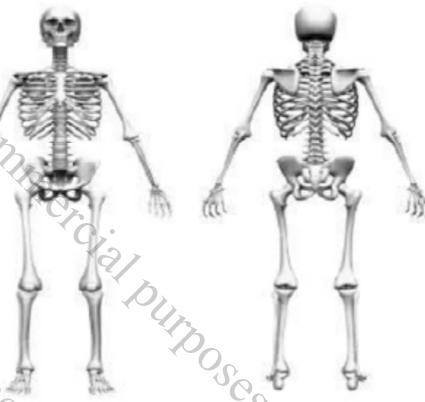
Page 91 of 95

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

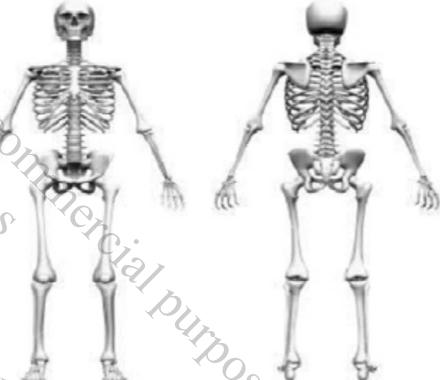
Page 92 of 95

Week 8 BASELINE Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input checked="" type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
<i>* Presence of new lesions at this time does not confirm progression</i>	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

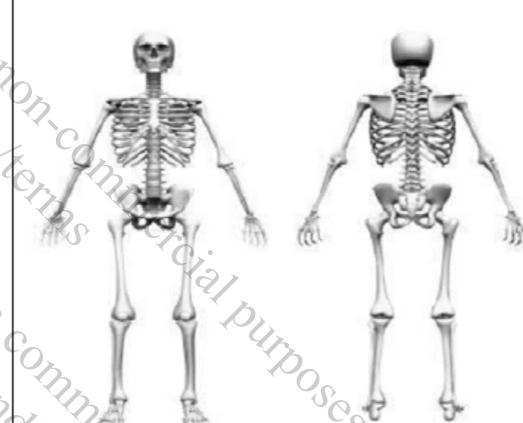
Page 93 of 95

Week 16 Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan:	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

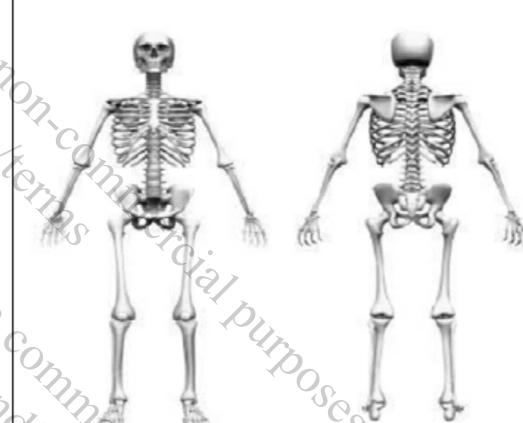
Page 94 of 95

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date:	<u>DD-MM-YYYY</u>
Is there radiolabeled tracer (e.g., ^{99m} Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 95 of 95

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date:	<u>D D - M M M - Y Y Y Y</u>
Is there radiolabeled tracer (e.g., ^{99m} Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan:	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?	<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 4.01 DE

Date: 08 July 09 August 2019

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)

133,925 or site equivalent (⁶⁸Ga PSMA-11)

EudraCT No. 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617; ⁶⁸Ga PSMA-11

Sponsor: Endocyte, Inc., A Novartis Company.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Page 2 of 115

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Protocol No./Acronym: [from Title page](#) PSMA-617-01
Version No.: [from Title page](#)
April4.1DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
01
23 July 2019

Page 3 of 115

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Protocol no. PSMA-617-01
Version no.:
4.0
[08 July 1 DE](#)

Endocyte, Inc., a Novartis Company

[09 August 2019](#)

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table of Contents

Site Principal Investigator Signature	3
Table of Contents	4
Revision History	13
Clinical Trial Summary	15
List of Abbreviations and Definitions	18
1. Introduction	20
1.1 Background information	20
1.2 Summary of nonclinical studies with clinical significance	24
1.3 Summary of known and potential risks and benefits	25
2. Trial Objectives and Endpoints	26
2.1 Trial objectives	26
2.1.1 Primary objective	26
2.1.2 Key secondary objectives	26
2.1.3 Additional secondary objectives	26
2.2 Trial endpoints	27
2.2.1 Alternate Primary endpoints	27
2.2.2 Key Secondary endpoints	27
2.2.3 Additional Secondary endpoints	27
3. Trial Design	28
3.1 Overview of the clinical trial design	28
3.1.1 Study design update	32
3.2 Rationale for the study design	33
3.3 Measures taken to minimize/avoid bias	33
3.4 Description of the clinical trial	33
3.4.1 Description of investigational medicinal product	33
3.4.2 Dosage and rationale for dose selection	34
3.4.3 Subject allocation to treatment	35
3.4.4 End of treatment visit	35
3.4.5 Duration of Subject Participation	35
3.5 End of trial definition	35
4. Selection and DISCONTINUATION of Subjects	36
4.1 Inclusion criteria	36
4.2 Exclusion criteria	38
4.3 Subject withdrawal of consent for study or treatment	39

Protocol no. PSMA-617-01

Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

5. Treatment of Subjects	39
5.1 Treatment with the investigational medicinal product	39
5.1.1 Administration of ⁶⁸ Ga PSMA-11	39
5.1.2 Administration of ¹⁷⁷ Lu PSMA-617	39
5.1.3 Toxicity risk reduction and supportive care for ¹⁷⁷ Lu PSMA-617 injections	40
5.1.4 Management of toxicity adverse events: dosing delays and modification	41
5.2 Best supportive/best standard of care	42
5.3 Concomitant medications/ supportive care	43
5.3.1 Permitted concomitant medications/ supportive care	43
5.3.2 Prohibited concomitant medications	44
5.4 Monitoring treatment compliance	44
5.5 Treatment discontinuation	44
6. Study Assessments and Procedures	45
6.1 Screening procedures and baseline assessments	45
6.2 Efficacy assessments	47
6.2.1 Radiographic imaging for tumor assessments	47
6.2.2 Additional Imaging Analyses	47
6.2.3 RECIST criteria	48
6.2.4 Symptomatic skeletal events	48
6.2.5 Pain score	48
6.2.6 Health related quality of life	48
6.2.7 Health Economics	49
6.2.8 Clinical progression	50
6.2.9 PSA levels	50
6.3 Safety assessments	50
6.3.1 Clinical laboratory evaluations	50
6.3.2 Vital signs	51
6.3.3 Electrocardiograms	51
6.3.4 Birth Control	51
6.4 End of treatment visit procedures	51
6.5 Long term follow up procedures	51
7. Adverse Events	52
7.1 Adverse event definitions	52
7.2 Evaluating and recording adverse events	53
7.3 Immediate Adverse Event Reporting	54

Protocol no. PSMA-617-01

Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

7.3.1	Serious Adverse Events	54
7.3.2	Serious adverse event subject follow up.....	54
7.3.3	Sponsor Contact Information for Immediate Reporting	55
8.	Statistics	55
8.1	Revision to the protocol and statistical analyses of rPFS and OS	55
8.2	Revisions to planned analyses	56
8.3	Sample size and power determination	56
8.4	Analysis populations	57
8.5	Demographics and baseline disease characteristics	57
8.6	Patient disposition	57
8.7	Efficacy analyses	58
8.7.1	Alternate primary endpoint efficacy analysis	58
8.7.2	Secondary efficacy analyses	59
8.8	Safety analyses	60
8.8.1	Extent of exposure	61
8.8.2	Analysis of adverse events	61
8.8.3	Analysis of laboratory assessments	61
8.8.4	Analysis of vital sign data	61
8.9	IDMC and Interim Data Evaluation	62
8.9.1	IDMC	62
8.9.2	Formal Interim Analysis of OS	62
9.	Access to Source Data/Documents	62
10.	Ethics	63
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	63
10.2	Informed consent	63
10.3	Health Insurance Portability and Accountability Act	63
10.4	Confidentiality	64
11.	Compliance and quality control	64
11.1	Compliance with Monitoring and Audits	64
12.	Data Handling, Record Keeping, and Compliance	65
12.1	Investigational medicinal product accountability	65
12.2	Breaking the blind	65
12.3	Data collection forms and source document identification	65
12.4	Record maintenance and retention	66

<u>12.5 Archiving</u>	66
<u>13 Publication Policy</u>	66
<u>14 References</u>	68
<u>Appendix 1 Schedules of Assessments</u>	75
<u>Appendix 2 Suggested treatment guidelines</u>	85
<u>Appendix 3 Principal Investigator Signature</u>	86
<u>Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	87
<u>Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison</u>	88
<u>Appendix 5 Common Terminology Criteria for Adverse Events</u>	89
<u>Appendix 6 Response Evaluation Criteria in Solid Tumors</u>	90
<u>Appendix 7 Prostate Cancer Working Group 3 Recommendations</u>	91
<u>Appendix 8 BPI-SF (sample only, not for patient use)</u>	93
<u>Appendix 9 EQ 5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (sample only, not for patient use)</u>	96
<u>Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (sample only, not for patient use)</u>	100
<u>Appendix 11 PCCTC Bone Scan Assessment Tool</u>	104
<u>Site Principal Investigator Signature</u>	13
<u>Table of Contents</u>	4
<u>Revision History</u>	13
<u>Clinical Trial Summary</u>	15
<u>List of Abbreviations and Definitions</u>	18
<u>1. Introduction</u>	20
<u>1.1 Background information</u>	20
<u>1.2 Summary of nonclinical studies with clinical significance</u>	24
<u>1.3 Summary of known and potential risks and benefits</u>	25
<u>2. Trial Objectives and Endpoints</u>	26
<u>2.1 Trial objectives</u>	26
<u>2.1.1 Primary objective</u>	26
<u>2.1.2 Key secondary objectives</u>	26
<u>2.1.3 Additional secondary objectives</u>	26
<u>2.2 Trial endpoints</u>	27
<u>2.2.1 Alternate Primary endpoint</u>	27

<u>2.2.2</u>	<u>Key Secondary endpoints.....</u>	<u>27</u>
<u>2.2.3</u>	<u>Additional Secondary endpoints</u>	<u>27</u>
<u>3.</u>	<u>Trial Design</u>	<u>28</u>
<u>3.1</u>	<u>Overview of the clinical trial design</u>	<u>28</u>
<u>3.1.1</u>	<u>Study design update</u>	<u>32</u>
<u>3.1.2</u>	<u>Study design update – Dosimetry, PK and ECG sub-study</u>	<u>32</u>
<u>3.2</u>	<u>Rationale for the study design</u>	<u>33</u>
<u>3.3</u>	<u>Measures taken to minimize/avoid bias</u>	<u>33</u>
<u>3.4</u>	<u>Description of the clinical trial</u>	<u>33</u>
<u>3.4.1</u>	<u>Description of investigational medicinal product</u>	<u>33</u>
<u>3.4.2</u>	<u>Dosage and rationale for dose selection.....</u>	<u>34</u>
<u>3.4.3</u>	<u>Subject allocation to treatment.....</u>	<u>35</u>
<u>3.4.4</u>	<u>End of treatment visit</u>	<u>35</u>
<u>3.4.5</u>	<u>Duration of Subject Participation.....</u>	<u>35</u>
<u>3.5</u>	<u>End of trial definition</u>	<u>35</u>
<u>4.</u>	<u>Selection and discontinuation of Subjects</u>	<u>36</u>
<u>4.1</u>	<u>Inclusion criteria.....</u>	<u>36</u>
<u>4.2</u>	<u>Exclusion criteria.....</u>	<u>38</u>
<u>4.3</u>	<u>Subject withdrawal of consent for study or treatment</u>	<u>39</u>
<u>5.</u>	<u>Treatment of Subjects</u>	<u>39</u>
<u>5.1</u>	<u>Treatment with the investigational medicinal product</u>	<u>39</u>
<u>5.1.1</u>	<u>Administration of ⁶⁸Ga-PSMA-11</u>	<u>39</u>
<u>5.1.2</u>	<u>Administration of ¹⁷⁷Lu-PSMA-617</u>	<u>39</u>
<u>5.1.3</u>	<u>Toxicity risk reduction and supportive care for ¹⁷⁷Lu-PSMA-617 injections</u>	<u>40</u>
<u>5.1.4</u>	<u>Management of toxicity adverse events: dosing delays and modification.....</u>	<u>41</u>
<u>5.2</u>	<u>Best supportive/best standard of care</u>	<u>42</u>
<u>5.3</u>	<u>Concomitant medications/ supportive care</u>	<u>43</u>
<u>5.3.1</u>	<u>Permitted concomitant medications/ supportive care</u>	<u>43</u>
<u>5.3.2</u>	<u>Prohibited concomitant medications</u>	<u>44</u>
<u>5.4</u>	<u>Monitoring treatment compliance</u>	<u>44</u>
<u>5.5</u>	<u>Treatment discontinuation</u>	<u>44</u>
<u>6.</u>	<u>Study Assessments and Procedures</u>	<u>45</u>
<u>6.1</u>	<u>Screening procedures and baseline assessments</u>	<u>45</u>
<u>6.2</u>	<u>Efficacy assessments</u>	<u>47</u>
<u>6.2.1</u>	<u>Radiographic imaging for tumor assessments</u>	<u>47</u>

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

<u>6.2.2 Additional Imaging Analyses.....</u>	47
<u>6.2.3 RECIST criteria.....</u>	48
<u>6.2.4 Symptomatic skeletal events</u>	48
<u>6.2.5 Pain score</u>	48
<u>6.2.6 Health-related quality of life</u>	48
<u>6.2.7 Health Economics</u>	49
<u>6.2.8 Clinical progression</u>	50
<u>6.2.9 PSA levels.....</u>	50
<u>6.3 Safety assessments.....</u>	50
<u>6.3.1 Clinical laboratory evaluations</u>	50
<u>6.3.2 Vital signs</u>	51
<u>6.3.3 Electrocardiograms</u>	51
<u>6.3.4 Birth Control</u>	51
<u>6.4 End of treatment visit procedures.....</u>	51
<u>6.5 Long-term follow-up procedures.....</u>	51
<u>7. Adverse Events.....</u>	52
<u>7.1 Adverse event definitions.....</u>	52
<u>7.2 Evaluating and recording adverse events</u>	53
<u>7.3 Immediate Adverse Event Reporting</u>	54
<u>7.3.1 Serious Adverse Events</u>	54
<u>7.3.2 Serious adverse event subject follow-up.....</u>	54
<u>7.3.3 Sponsor Contact Information for Immediate Reporting</u>	55
<u>8. Statistics.....</u>	55
<u>8.1 Revision to the protocol and statistical analyses of rPFS and OS</u>	55
<u>8.2 Revisions to planned analyses</u>	56
<u>8.3 Sample size and power determination.....</u>	56
<u>8.4 Analysis populations</u>	57
<u>8.5 Demographics and baseline disease characteristics</u>	57
<u>8.6 Patient disposition</u>	57
<u>8.7 Efficacy analyses</u>	58
<u>8.7.1 Alternate primary endpoint analysis</u>	58
<u>8.7.2 Secondary efficacy analyses</u>	59
<u>8.8 Safety analyses</u>	60
<u>8.8.1 Extent of exposure</u>	61
<u>8.8.2 Analysis of adverse events</u>	61

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

<u>8.8.3</u>	<u>Analysis of laboratory assessments.....</u>	<u>61</u>
<u>8.8.4</u>	<u>Analysis of vital sign data.....</u>	<u>61</u>
<u>8.9</u>	<u>IDMC and interim data evaluation</u>	<u>62</u>
<u>8.9.1</u>	<u>IDMC</u>	<u>62</u>
<u>8.9.2</u>	<u>Formal interim analysis of OS</u>	<u>62</u>
<u>9.</u>	<u>Access to Source Data/Documents.....</u>	<u>62</u>
<u>10.</u>	<u>Ethics</u>	<u>63</u>
<u>10.1</u>	<u>Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB).....</u>	<u>63</u>
<u>10.2</u>	<u>Informed consent</u>	<u>63</u>
<u>10.3</u>	<u>Health Insurance Portability and Accountability Act.....</u>	<u>63</u>
<u>10.4</u>	<u>Confidentiality</u>	<u>64</u>
<u>11.</u>	<u>Compliance and quality control.....</u>	<u>64</u>
<u>11.1</u>	<u>Compliance with Monitoring and Audits</u>	<u>64</u>
<u>12.</u>	<u>Data Handling, Record Keeping, and Compliance</u>	<u>65</u>
<u>12.1</u>	<u>Investigational medicinal product accountability.....</u>	<u>65</u>
<u>12.2</u>	<u>Breaking the blind</u>	<u>65</u>
<u>12.3</u>	<u>Data collection forms and source document identification</u>	<u>65</u>
<u>12.4</u>	<u>Record maintenance and retention</u>	<u>66</u>
<u>12.5</u>	<u>Archiving</u>	<u>66</u>
<u>13.</u>	<u>Publication Policy.....</u>	<u>66</u>
<u>14.</u>	<u>References</u>	<u>68</u>
<u>Appendix 1</u>	<u>Schedules of Assessments</u>	<u>75</u>
<u>Appendix 2</u>	<u>Suggested treatment guidelines</u>	<u>85</u>
<u>Appendix 3</u>	<u>Principal investigator signature</u>	<u>86</u>
<u>Appendix 4a</u>	<u>Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....</u>	<u>87</u>
<u>Appendix 4b</u>	<u>Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison.....</u>	<u>88</u>
<u>Appendix 5</u>	<u>Common Terminology Criteria for Adverse Events</u>	<u>89</u>
<u>Appendix 6</u>	<u>Response Evaluation Criteria in Solid Tumors</u>	<u>90</u>
<u>Appendix 7</u>	<u>Prostate Cancer Working Group 3 Recommendations</u>	<u>91</u>
<u>Appendix 8</u>	<u>BPI-SF (<i>sample only, not for patient use</i>).....</u>	<u>93</u>
<u>Appendix 9</u>	<u>EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>).....</u>	<u>96</u>

<u>Appendix 10</u> FACT-P (Functional Assessment of Cancer Therapy – Prostate) (sample only, not for patient use).....	100
<u>Appendix 11</u> PCCTC Bone Scan Assessment Tool.....	104
<u>Appendix 12</u> Dosimetry, PK and ECG Sub- study	111
<u>1. DOSIMETRY, PK and ECG SUB-STUDY DESIGN</u>	111
<u>2. Objectives</u>	111
<u>2.1 Primary Objective:</u>	111
<u>2.2 Secondary Objectives:</u>	111
<u>3. DOSIMETRY, PK and ECG SUB-STUDY ASSESSMENTS</u>	111
<u>3.1 Imaging Assessments</u>	112
<u>3.1.1 Equipment</u>	112
<u>3.2 PK Blood Sampling</u>	112
<u>3.3 Cardiac Assessments</u>	113
<u>3.4 Urine</u>	113
<u>3.5 Measurements, Recording, Calculation and Analysis of Sub-study Data</u>	115

List of tables

<u>Table 1</u> Toxicity management and dose modification recommendations.....	41
<u>Table 2</u> Screening procedures and baseline assessments	45
<u>Table 3</u> Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1).....	76
<u>Table 4</u> Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)	78
<u>Table 5</u> Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1)	81
<u>Table 6</u> Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU)	83
<u>Table 1</u> Toxicity management and dose modification recommendations.....	41
<u>Table 2</u> Screening procedures and baseline assessments	45
<u>Table 3</u> Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1).....	76
<u>Table 4</u> Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)	78

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 12 of 115

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) – (Not applicable for V4.1 DE).....	81
Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) – (Not applicable for V4.1 DE).....	83

List of figures

Figure 1 Diagram of trial design	30
Figure 1 Diagram of trial design	30

Protocol no. PSMA-617-01
Version no.:
4.0
[08 July 1 DE](#)

Endocyte, Inc., a Novartis Company.

[09 August 2019](#)

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment: AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment: AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added.• Updated reference section
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 2019 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

		<ul style="list-style-type: none">• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.• Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.• Additional imaging analyses details were added for study ⁶⁸Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.• Further clarification on the start and end timing for ⁶⁸Ga-PSMA-11 TEAEs, ¹⁷⁷Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.• Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression.
4.1	09 August 2019	<p>DE amendment – all protocol changes noted above for Versions 2, 3 and 4 are also included in DE amendment 4.1</p> <p>Added a dosimetry, pharmacokinetics (PK) and electrocardiogram (ECG) sub-study which will include a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients from selected sites in Germany. Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.</p>

Protocol no. PSMA-617-01
Version no.:

4.0

[08 July 1 DE](#)

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

[09 August 2019](#)

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare the two alternate primary endpoints of radiographic progression-free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.• Dosimetry, PK and ECG in a sub-study of approximately 30 patients
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of adverse events (AEs) related to the natural course of the disease, as well as pre-existing AEs and study related AEs.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</p> <p>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up.</p> <p>A long-term follow-up period will include the collection of rPFS survival and information about new treatments, along with the patient's response to these</p>

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

	<p>treatment updates, adverse events assessment, and as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (± 1 month) via phone, email, or letter for up to 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).</p> <p>These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 814 patients.</p> <p>A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617.</p> <p>In order to not bias the results obtained from randomized patients in the main study, the data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The sub-study details and analyses will be presented in a separate report.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

	<p><u>Patients included in the sub-study will receive the investigation arm (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care).</u></p>
Assessment schedule:	<p>Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit.</p> <p>The previous 2 PSA values will be noted before randomization. Serum <u>plasma</u> testosterone and PSA levels will be measured <u>up-to-within</u> 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (<u>up-to-within</u> 3 days prior to each time point) and <u>up-to-within</u> 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6 (i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every <u>128</u> weeks (± 4 days <u>1 week</u>) until the patient starts long term follow up.</p> <p>Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.</p> <p><u>Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management of patients in the sub-study will remain identical to that implemented in the main study.</u></p>
Statistical methodology:	<p>Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5th, 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final analysis of OS will be performed when 508 <u>deaths/death events</u> have accrued and the alpha level applied will be 0.02 1-sided. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.</p> <p>This trial has at least 90% overall power and an overall Type I error rate of at most 0.025 1-sided.</p>
Duration of Study:	Total duration of the study will be approximately 38 months.

Protocol no. PSMA-617-01

Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BfS	Federal Office for Radiation Protection (Bundesamt für Strahlenschutz)
BPI-SF	Brief Pain Inventory - Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DE	Germany
DOT	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQoL) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPLC	High pressure liquid chromatography
HR	Hazard ratio
hr	hour
HRQoL	Health-related quality of life

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Abbreviation	Term/Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
<u>Min(s)</u>	<u>Minute(s)</u>
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
<u>SPEC</u>	<u>Single-photon emission computed tomography</u>
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol.

The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Ferlay et al 2013, Bray et al 2012).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men (Siegel et al 2017), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months (Smith et al 2016). Post-docetaxel mCRPC patients have an annual death rate of 73% (Scher et al 2015).

The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases (Kirby et al 2011), and 49% of them will develop a serious skeletal event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005). These patients, many of whom are elderly, can be

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 2018 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in [43%](#) to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#), [Cheng et al 2015](#), [Badrising et al 2014](#), [Brasso et al 2015](#), [Loriot et al 2013](#), [Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#), [Ghosh and Heston 2004](#), [Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al](#)

[2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell ([Rajasekaran et al 2003](#)). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies ([Haberkorn et al 2016](#)).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance ([Benešová et al 2015](#)). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium-energy β^- -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y ([Emmett et al 2017](#)). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer ([Kratochwil et al 2015](#), [Hillier et al 2009](#)). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 23 of 115

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile and promising results for PSA response rates of systemic radioligand therapy with ¹⁷⁷Lu-PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ¹⁷⁷Lu-PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in [the prospective study compassionate use studies](#) xerostomia appears low grade and occurs at a rate of approximately [87%](#) in treated patients. Clearance of ¹⁷⁷Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to [67%](#) respectively.

The first published clinical series of ¹⁷⁷Lu-PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ¹⁷⁷Lu-PSMA-617 in [5030](#) metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018, Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ¹⁷⁷Lu-PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective [overall](#) response rate [in measurable disease](#) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ¹⁷⁷Lu-PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ¹⁷⁷Lu-PSMA-617 in patients who have been exposed to approved agents. In

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1-2, of ^{177}Lu -PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. -The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ^{177}Lu -PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ^{177}Lu -PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ^{177}Lu -PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 μg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-

effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). -The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27-fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 670% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4-8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Page 26 of 115

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include:
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
 2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
 3. Health Economics
 4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
 5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG (sub-study of approximately 30 patients).

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

2.2 Trial endpoints

2.2.1 Alternate Primary endpoint

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.

Page 28 of 115

- a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
- b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression
 - Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
- c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.

5. Biochemical response endpoints:

- a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
- b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.

6. Dosimetry, PK, and ECG in a sub-study of approximately 30 patients

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in

Protocol no. PSMA-617-01
Version no.:
4.0

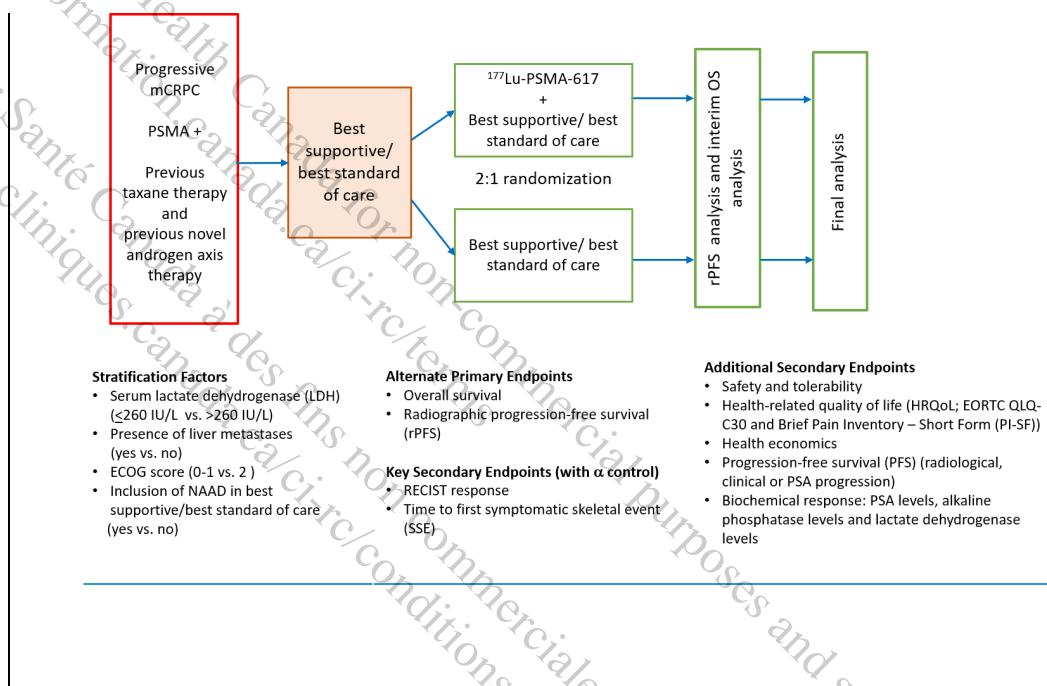
08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).



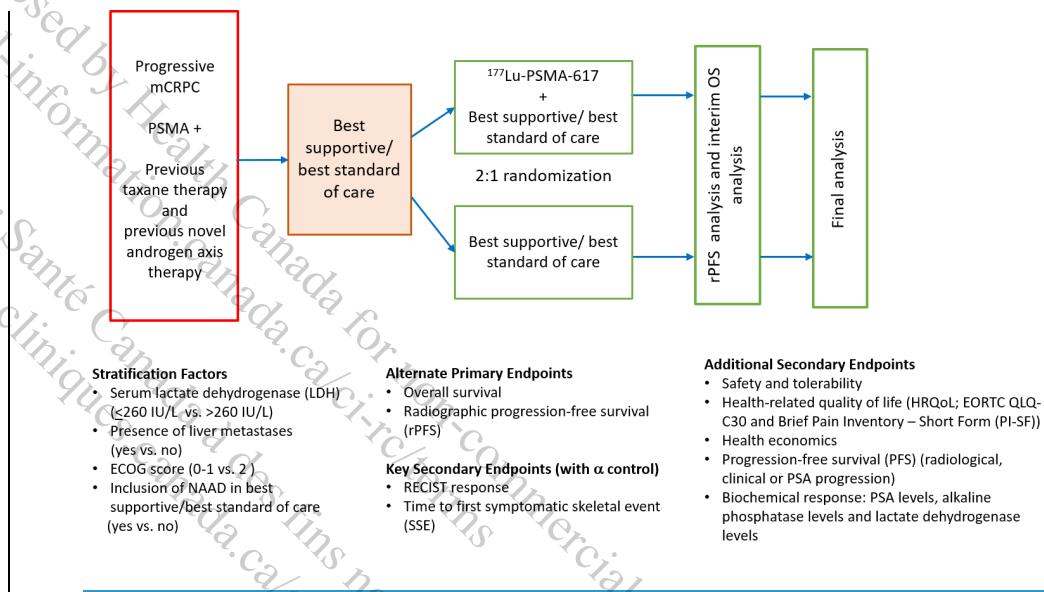


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment -for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for up-to 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 2018 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.1.2 Study design update – Dosimetry, PK and ECG sub-study

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

In order to not bias the results obtained from randomized patients in the main study, the data of the substudy patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The substudy details and analyses will be presented in a

separate report. Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific tests conducted in the sub-study, as described in Appendix 12, and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. -Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms, with exception to the additional 30 patients in the sub-study who will receive the investigational treatment. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu -PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. -The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). -PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu -PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu -PSMA-617 is well tolerated according to the clinical experience that has been documented in 4224 publications, summarizing the safety and or efficacy information from over 800500 subjects. Across these studies doses have ranged from 4.1-122.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-98 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. -However, efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018, Kulkarni et al 2018, Bräuer et al 2017, Yordanova et al 2017). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu -PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu -PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu -PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu -PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) or the best supportive/best standard of care-only arm using a permuted block scheme. Patients included in the sub-study will not undergo randomization as all patients will receive the investigational arm.

Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care at time of randomization (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

It is anticipated that it will take approx.-approximately 14 months to randomize the required 814 patients in the study. After the last patient is randomized, patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. Long-term follow up for safety and survival will continue for up to 24 months per patient. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must behave a positive ^{68}Ga -PSMA-11 PET/CT scan positive, and eligible, as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 2018 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

- a. Serum/plasma PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).
14. Patients must have adequate organ function:
- a. Bone marrow reserve:
 - White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
 - Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
 - Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)
 - b. Hepatic:
 - Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases
 - c. Renal:
 - Serum/plasma creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$
15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L).
- [Inclusion #16 has been removed]
16. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible.

16.17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

17.18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 63 months after last study drug administration.

18.19. The best standard of care/ best supportive care options planned for this patient:
a. Are allowed by the protocol.
b. Have been agreed to by the treating investigator and patient.
c. Allow for the management of the patient without ¹⁷⁷Lu-PSMA-617.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 2018 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the randomized treatment arm in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga -PSMA-11

For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure. The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

[Refer to the Fendler et al 2017 publication “ \$^{68}\text{Ga}\$ PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of \$^{68}\text{Ga}\$ -PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.](#)

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 40 of 115

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with ≥ 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(+/- 5) minutes before and at 30(+/- 5) and 60(+/- 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (\pm 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. **Table 1** provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count $<3.0 \times 10^9/\text{L}$• ANC $<1.5 \times 10^9/\text{L}$	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematocrit levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.
Thrombocytopenia (platelet count of $< 75 \times 10^9/\text{L}$)	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Hematological Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Hold ^{177}Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ^{177}Lu -PSMA-617 dose by 20% on the next cycle
Serum/plasma creatinine increased $\geq 40\%$ from baseline AND calculated		Reduce ^{177}Lu-PSMA-617 dose by 20% on the next cycle

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
creatinine clearance decreased >40% from baseline		
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity (not amenable to medical intervention)	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline Reduce ¹⁷⁷Lu-PSMA-617 dose by 20% on the next cycle
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 128 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company.

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm should/will be administered as per physician's orders and protocol at the institution, and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section [5.1.45.1.4](#) for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, or other systemic radio isotopes (e.g., radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

If a patient discontinues the treatment part of the study for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization ([enrollment for sub-study patients](#)) except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. -Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Adverse Event (AE) monitoring and Serious Adverse Event (SAE) reporting	Begins at time of consent
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
	The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool or equivalent to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum/ plasma testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks (+ 2 weeks) of start of treatment but not within the 6 days prior to start of treatment. StudyPSMA eligibility based on PSMA positivity will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

Endocyte, Inc., [a Novartis Company](#).

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu -PSMA-617 within 28 days after randomization.

^a For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1. The timing of the additional assessments for the sub-study are provided in Appendix 12.](#)

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ^{68}Ga -PSMA-11 scan data will be used for additional exploratory analyses. The ^{68}Ga -PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ^{68}Ga -PSMA-11 PET/CT scans by

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ⁶⁸Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ⁶⁸Ga-PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints -will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

6.2.5 Pain score

Pain will be assessed using the [Brief Pain Inventory – Short Form \(BPI-SF\)](#).

The [Brief Pain Inventory – Short Form \(BPI-SF\)](#) will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL Group 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being (Cella et al 1993). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies (Cella et al 1993, Esper et al 1997)
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format (Webster et al 2003)

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) [sub-study analysis](#) will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 50 of 115

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum/plasma testosterone, and urinalysis testing.

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 51 of 115

Chemistry, urinalysis, and hematology testing will include the following:

Chemistry	<ul style="list-style-type: none">● <u>sodium</u>● potassium● total and direct bilirubin● ALP● AST● ALT	<ul style="list-style-type: none">● LDH● blood urea nitrogen^{**}● creatinine● uric acid● phosphorus● chloride	<ul style="list-style-type: none">● bicarbonate*● calcium● glucose● total protein● albumin
Urinalysis	<ul style="list-style-type: none">● urine pH● protein content● specific gravity● appearance and color	<ul style="list-style-type: none">● glucose● ketones	
Hematology	<ul style="list-style-type: none">● complete blood count (white blood cell count and differential)● red blood cell count● hemoglobin● hematocrit● platelet count●		

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g., condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least ⁶³ months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter.

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 52 of 115

Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Term	Definitions ^a
Adverse Event (AE)	<p>Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p> <p>Progression of disease is not considered an AE or SAE for this study.</p>
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	<p>A serious adverse event or reaction is any untoward medical occurrence that at any dose:</p> <ul style="list-style-type: none">• results in death; except for deaths due to progression of disease• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p>
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11, [and/or](#) ¹⁷⁷Lu-PSMA-617, [and/or best supportive/best standard of care](#), will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11, [and/or](#) ¹⁷⁷Lu-PSMA-617, [and/or best supportive/best standard of care](#). AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11, [and/or](#) ¹⁷⁷Lu-PSMA-617, [and/or best supportive/best standard of care](#) will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 2018 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc. [a Novartis Company](#)

09 August 2019

Page 54 of 115

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11, and/or ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is “unknown and of questionable relationship to the study drug” the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is “unknown but not related to the study drug” the determination and rationale will be documented in the patient’s case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ⁶⁸Ga-PSMA-11, and/or ¹⁷⁷Lu-PSMA-617, and/or best supportive/best standard of care; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 55 of 115

investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc. [a Novartis Company](#)

09 August 2019

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non- confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

| For rPFS, a total of approximately 557/814 patients are expected to be randomized ~~on~~ or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341 deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p < 0.004$ 1-sided is achieved for rPFS and $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p < 0.004$ 1-sided is achieved for rPFS but $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.

- if $p < 0.004$ 1-sided is not achieved for rPFS but $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS and $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p < 0.020$ to $p < 0.025$ in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 58 of 115

- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint [efficacy](#)-analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. [The PFS events](#) The primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, -stratified for the randomization stratification factors....

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Protocol no. PSMA-617-01
Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS or OS at the respective allocated alpha level; it is not required to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level or OS to meet its allocated alpha level at either (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) or (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level

applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ^{177}Lu -PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG in a sub-study of approximately 30 patients presented separately from the main study analyses.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value.-DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by Ellis et al 2008.

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set. The same analyses will be performed separately in the sub-study of approximately 30 patients.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ⁶⁸Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ⁶⁸Ga-PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ⁶⁸Ga-PSMA-11 dosing up to 6 days after the date of ⁶⁸Ga-PSMA-11 dosing as long as prior to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ⁶⁸Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ⁶⁸Ga-PSMA-11 TEAEs. Unrelated ⁶⁸Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

| **[Adverse events](#)AEs** leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and Interim Data Evaluation-interim data evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal Interim Analysis-interim analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. - Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte

Protocol no. PSMA-617-01
Version no.:
4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 65 of 115

will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

Protocol no. PSMA-617-01
Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Page 67 of 115

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.:
4.0
08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015; 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bräuer et al 2017

Bräuer A, Grubert LS, Roll W, Schrader AJ, Schäfers M, Bögemann M, et al. ¹⁷⁷Lu-PSMA-617 radioligand therapy and outcome in patients with metastasized castration-resistant prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017 Sep;44(10):1663-70.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Protocol no. PSMA-617-01

Version no.:

4.0

08-July-1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. *Cancer Res.* 2009;69(17), 6932–40.

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. *Lancet Oncol.* 2018 Jun;19(6):825–833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2019;37(suppl 7S): 228.

Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract.* 2011 Nov;65(11):1180–92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research.* 2018 Jul;78(13):CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(6):987–88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170–1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Annals of Oncology 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Annals of Oncology 2013 24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. Clin Nucl Med. 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. J Nucl Med. 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfar J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. J Nucl Med. 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfar H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. Eur J Nucl Med Mol Imaging. 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXXXX Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate resistant prostate cancer (mCRPC): An initial experience in Jaslok. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res.* 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. *J Natl Cancer Inst.* 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. *PLoS One.* 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. *J Clin Oncol.* 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. *J Clin Oncol.* 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. *Health Qual Life Outcomes.* 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. *Eur J Nucl Med Mol Imaging.* 2016;43(Suppl 1):S213 EPW14.

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. *Ann Oncol.* 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. 177Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. *Eur J Nucl Med Mol Imaging.* 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2017; DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesely S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. *Can Urol Assoc J.* 2014 Jul;8(7-8):E520-3.

Page 75 of 115

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01

Version no.:

4.0

08 July 1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company

09 August 2019

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X-----					X-----
AE monitoring ^a	X-----					X-----
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X-----					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum plasma testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to within 3 days of Day 1) and at 15 (\pm 5) minutes before, 30 (\pm 5)-minutes post, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

| AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

| Protocol no. PSMA-617-01
Version no.: 4.0
DE

| Endocyte, Inc., a Novartis Company.
09 August 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

08 July 1

Table 4. Schedule of assessments: ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Table 4. Schedule of assessments: ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	^a						^a	X	
AE monitoring ^b	^a						^a	X	
Weight	X ^c						X ^e	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ¹⁷⁷ Lu-PSMA-617	X								
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	

Protocol no. PSMA-617-01

Version no. 4.0

DE

Endocyte, Inc., a Novartis Company.

08 July 1

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Inserted

Merged C

Deleted C

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks $(\pm 4 \text{ days})$		Every 3 months $(\pm 1 \text{ month})$
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	<u>X</u> <u>X</u> <u>X*</u>						<u>X^a</u>	X	
AE monitoring ^b	<u>X</u> <u>X</u> <u>X*</u>						<u>X^a</u>	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Serum plasma testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks ($\pm 4 \text{ days}$) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks ($\pm 4 \text{ days}$)								

Protocol no. PSMA-617-01
Version no. 4.0
DE

Endocyte, Inc., a Novartis Company.

08 July 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Collect:

- Hematology
- Chemistry
- Survival
- New treatment:
 - Start/stop dates
 - Best response
 - Type of response
 - AE assessment
- Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression)

Inserted

Deleted

- * After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:
 - The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
 - Has signs of residual disease on CT with contrast/MRI or bone scan and
 - has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone.

** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

a Phone evaluations are valuation is allowed, but are not required for visits after Day 1 of each cycle.

b Adverse event monitoring will commence at time of consent._

c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up towithin 3 days prior to Days 1, 15, and 29.

d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up towithin 3 days of Day 1) and at 15 (+/- 5) minutes before, 30 (+/- 5) minutes post, and 60 (+/- 5) minutes post ^{177}Lu -PSMA-617 administration.

e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (\pm 4 days).

g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study._

h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker_or clinician, or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell.

Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) – (Not applicable for V4.1 DE)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X				XX	X
AE monitoring ^b	X				XX	X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum/plasma testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after Cycle 1 Day 1*first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will commence at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01

Version no. 4.0

DE

Endocyte, Inc., a Novartis Company.

08 July 1

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Protocol no. PSMA-617-01
Version no.: 4.0
DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc., a Novartis Company.
09 August 2019

08 July 1

Table 6. Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) – (Not applicable for V4.1 DE)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	<u>X</u> <u>X</u> <u>X</u>						<u>X^a</u>	X	
AE monitoring ^b	<u>X</u> <u>X</u> <u>X</u>						<u>X^a</u>	X	
Weight	<u>X^c</u>						<u>X^eX^b</u>	X	
ECOG	<u>X^c</u>						<u>X^eX^b</u>	X	
Directed physical exam	<u>X^c</u>						<u>X^eX^b</u>	X	
Vital signs ^d signs ^c	<u>X^c</u>						<u>X^eX^b</u>	X	
EQ-5D-5L	<u>X^eX^{c,h}</u>						<u>X^{e,h}X^{d,g}</u>	<u>X^bX^{d,g}</u>	
FACT-P	<u>X^{e,h}</u>						<u>X^{e,h}X^{d,g}</u>	<u>X^bX^{d,g}</u>	
BPI-SF	<u>X^{e,h}</u>						<u>X^{e,h}X^{d,g}</u>	<u>X^bX</u>	
Best supportive/best standard of care	As per physician's orders								
Hematology ^e Hematology ^e	<u>X^c</u>		<u>X^eX^b</u>		<u>X^eX^b</u>		<u>X^b</u>	X	
Chemistry ^f Chemistry ^e	<u>X^c</u>		<u>X^eX^b</u>		<u>X^eX^b</u>		<u>X^b</u>	X	
Serum/plasma testosterone	<u>X^c</u>						<u>X^b</u>	X	

Protocol no. PSMA-617-01
Version no. 4.0
DE

Endocyte, Inc., a Novartis Company.

08 July 1

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Merged C
Deleted C

PSA	X ^c					X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)						To be conducted every 8 weeks (\pm 4 days) after Cycle 1 Day 1 first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)		

Deleted C

^{**}Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

^a Phone [evaluations](#) are allowed, but are not required for visits after Day 1 of each cycle.^{_}

^b Adverse event monitoring will commence at time of consent.

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice.
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment.
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Protocol no. PSMA-617-01
Version no.:
4.0
08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 86 of 115

Appendix 3 Principal Investigator Signature/investigator signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Protocol no. PSMA-617-01
Version no.:
4.0
08 July 1 DE

Endocyte, Inc., a Novartis Company

09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 89 of 115

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 90 of 115

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Record outcome as new lesions, no new lesions or resolved lesion• First scheduled reassessment:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ New lesions: perform a confirmatory scan 6 or more weeks later• Confirmatory scan:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ Additional new lesions: progression• Subsequent scheduled reassessments:<ul style="list-style-type: none">◦ No new lesions: continue◦ New lesions: progression• Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">• Exclude pseudoprogression in the absence of symptoms or other signs of progression• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented• For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan• Date of progression is the date of the scan that first documents the second lesion• Changes in intensity of uptake alone do not constitute either progression or regression• Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 93 of 115

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Brief Pain Inventory (Short Form)

Time: _____ : _____ AM PM

Today's Date (day, month, year):
_____-_____-_____
Day JAN FEB MAR APR JUN JUL AUG SEP OCT NOV DEC Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Page 95 of 115

Today's Date (Day, Month, Year): <u> </u> - <u> </u> - <u> </u> (Example: 08-FEB-2016) <u> </u> DAY <u> </u> MONTH <u> </u> YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01-April4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 97 of 115



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 98 of 115

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

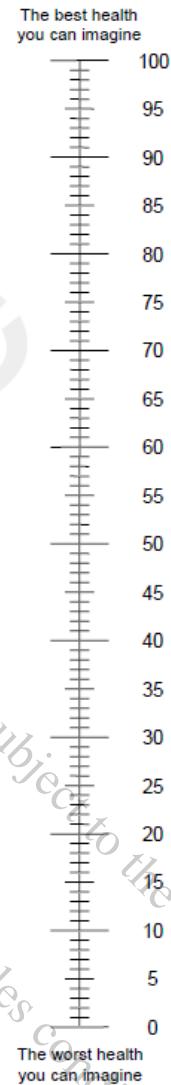
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 99 of 115

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01-April-4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 100 of 115

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy –
Prostate) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

GE1
GE2
GE3
GE4
GE5
GE6

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness.....	0	1	2	3	4
I am losing hope in the fight against my illness.....	0	1	2	3	4
I feel nervous.....	0	1	2	3	4
I worry about dying.....	0	1	2	3	4
I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

GF1
GF2
GF3
GF4
GF5
GF6
GF7

	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling.....	0	1	2	3	4
I am able to enjoy life.....	0	1	2	3	4
I have accepted my illness.....	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun.....	0	1	2	3	4
I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 104 of 115

Appendix 11 PCCTC Bone Scan Assessment Tool

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 3.0
DE

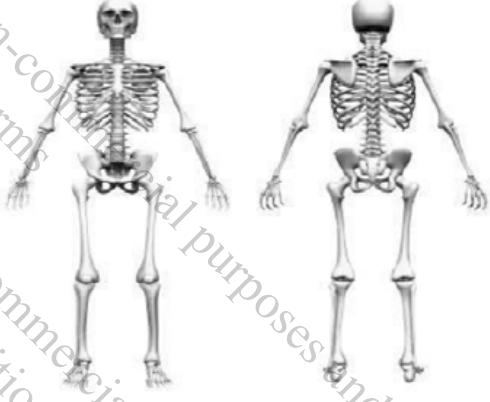
Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 8 BASELINE Scan

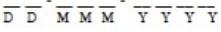
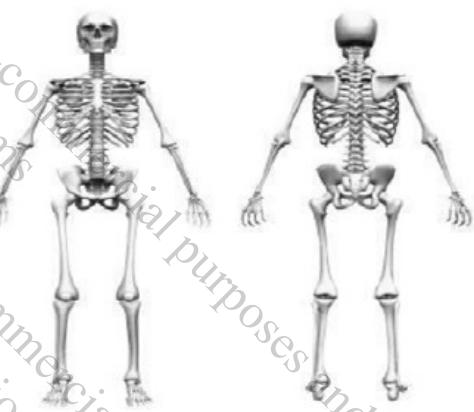
Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5
Check Region(s) of NEW Disease Post-Screening:	Draw site(s) of NEW lesion(s) on skeleton:  <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
* Presence of new lesions at this time does not confirm progression	
Clinical Impression:	<input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

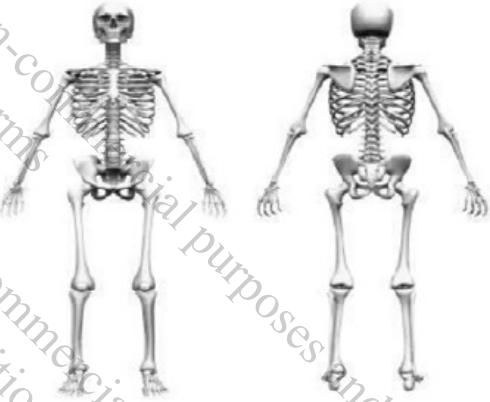
Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 108 of 115

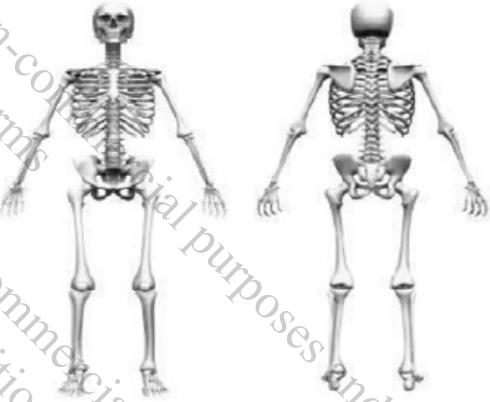
Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 109 of 115

Week <input type="checkbox"/> 24 <input type="checkbox"/> 36 <input type="checkbox"/> 48 <input type="checkbox"/> 60 <input type="checkbox"/> 72 <input type="checkbox"/> 84 <input type="checkbox"/> ____ Scan							
Bone Scan Date:		D D - M M M - Y Y Y Y					
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?		<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]					
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5							
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities		Draw site(s) of NEW lesion(s) on skeleton: 					
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?		<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]					
Does this bone scan confirm (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?		<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]					
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression							
Comments regarding the image (if needed):							
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:							

Page 110 of 115

Week <input type="checkbox"/> 24 <input type="checkbox"/> 36 <input type="checkbox"/> 48 <input type="checkbox"/> 60 <input type="checkbox"/> 72 <input type="checkbox"/> 84 <input type="checkbox"/> ____ Scan							
Bone Scan Date:		D D - M M M - Y Y Y Y					
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?		<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]					
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5							
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities		Draw site(s) of NEW lesion(s) on skeleton: 					
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?		<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]					
Does this bone scan confirm (2+2) the presence of 2 or more new lesions seen since the Week 8 Bone Scan?		<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]					
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression							
Comments regarding the image (if needed):							
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:							

APPENDIX 12 DOSIMETRY, PK AND ECG SUB-STUDY

1. DOSIMETRY, PK AND ECG SUB-STUDY DESIGN

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study.

Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific assessments conducted in the sub-study, as described below and the separate sub-study manual, the treatment regimen and patient care management will be identical to that implemented in the main study.

The results of this sub-study will be included in a Dosimetry Study Report addendum that will accompany the main study report.

2. OBJECTIVES

To evaluate dosimetry, pharmacokinetics, and ECG.

2.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ¹⁷⁷Lu-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney and bone marrow)

2.2 Secondary Objectives:

- Define the pharmacokinetic profile of ¹⁷⁷Lu-PSMA-617;
- Evaluate ECGs during treatment with ¹⁷⁷Lu-PSMA-617;
- Evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617;
- Evaluate the metabolic stability of ¹⁷⁷Lu-PSMA-617

3. DOSIMETRY, PK AND ECG SUB-STUDY ASSESSMENTS

The sub-study patients will require full body (planar) and 3D SPECT/CT imaging, blood PK sampling and ECGs, during cycle 1 of treatment. Urine will be collected for HPLC (High-performance liquid chromatography) analysis.

Refer to Table 7 and the sub-study manual for timing assessments.

3.1 Imaging Assessments

Baseline images will be used to determine volumes in regions of interest in selected major source organs such as the liver, spleen and kidneys. Refer to the sub-study manual for further details on measurements and calculations.

Serial gamma camera images (whole body planar images) will be obtained in the first treatment cycle detailed in table 7 below. 3D SPECT/CT scans will be also performed in the upper abdomen (comprising kidneys, liver and spleen).

Full body planar images will be acquired at the following time points after administration:

- 1-2 hours
- 18-26 hours
- 36-48 hours
- 156-168 hours

3D SPECT images will be acquired at the following time points after administration:

- 1-2 hours (Additional CT imaging required)
- 18-26 hours
- 36-48 hours
- 156-168 hours

3.1.1 Equipment

The following equipment will be required:

1. A gamma-camera with medium energy collimator.
2. A Co-57 flood source or a Lu-177 or Tc-99m filled flood source for the transmission scan. Well counter with multichannel analyzer or gamma counter to determine ¹⁷⁷Lu radioactivity in blood and urine samples.
3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.

3.2 PK Blood Sampling

Blood PK samples will be collected during cycle 1 of the treatment, to provide data for bone marrow radiation dose calculations and for PK assessment.

At cycle 1, blood samples (1mL) will be collected in heparinized tubes starting immediately before the start of administration, end of administration, then approximately 20mins (+/- 5mins), 60mins(+/- 5mins), 2hr (+/- 30mins), 4hr (+/- 30mins), 24hr (+/- 2hrs), 48hr (+/- 2hrs), 72hr (+/-

2hrs) & day 6 post end of infusion. Blood PK samples should be collected after ECGs, where timepoints overlap. Refer to Table 7 for the timing of assessments.

Radioactivity in blood will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time points have to be recorded by site. The exact time point of each measurement and the calibration factor must be documented by the investigational site.

3.3 Cardiac Assessments

A twelve-lead ECG test will be performed in triplicate for all patients during Cycle 1 of treatment for up to 4 time points (pre-administration and thereafter at approximately 1hr, 4hrs and 24hrs post treatment). Blood Pressure (BP) should be measured prior to each ECG time point.

Patients should have a light breakfast on the morning of treatment.

In the event of a clinically significant finding (i.e., QTcF increase from baseline of >30ms occurs), an additional single safety ECG should be repeated prior to dosing at cycle 2.

All pre-medications will be administered during the time interval ranging from 90 mins to 60 mins before the start of infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen.

If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1hr before the start of infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1hr before, until 8hr after the start of infusion, unless clinically required.

Data obtained will be analyzed by a central reader to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Clinically significant abnormalities will be recorded on the Adverse Event page of the eCRF.

ECG parameters will include HR, RR interval, PR interval, QRS interval and QT interval. QT intervals will be corrected for HR.

3.4 Urine

Total urine excreted will be collected between the end of infusion and the time of the first image (2hrs post infusion).

The extent of elimination of the radiolabeled compound must be determined before acquiring the first image. Therefore, the urine eliminated between the infusion and the time of the first image must be collected quantitatively (possibly in one single container), the whole volume or mass of this excreted urine must be measured and 1 mL sample withdrawn for radioactivity measurement. Radioactivity in urine will be measured at the investigational site, with a properly

Protocol no. PSMA-617-01

Version no.: 3.0

DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

01 April 4.1

09 August 2019

calibrated gamma counter or similar system. The exact time point of urine collection and measurement, as well as the calibration factor must be documented by the investigational site.

An aliquot (10 mL) of the whole urine collected between the infusion and the time of the first image will be also sent to a central laboratory for HPLC analysis. Moreover, for HPLC analysis purpose only, additional urine samples (around 10 mL, no need to have cumulative urine samples for this assessment) will be collected from the patients at 24hrs (+/-2hrs), 48hrs (+/-2hrs) and 72hrs (+/-2hrs). Collected samples will be sent to a central laboratory for analysis by HPLC according to a validated procedure, in order to determine the elimination of the radioactive compound and possible metabolites, if any, over time.

Table 7: Sub-Study Assessment timepoints (Cycle 1 only)

	<u>Planar full body imaging</u>	<u>3D SPECT imaging</u>	<u>Blood sampling</u>	<u>BP & Intense ECG^{b,d}</u>	<u>Urine</u>
<u>Pre dose</u>			X	X	
<u>End of dose</u>			X		
<u>20 mins</u> <u>(+/- 5 mins)</u>			X		
<u>60 mins</u> <u>(+/- 5 mins)</u>			X	X	
<u>2 hours</u>	<u>X (1-2 hours)^c</u>	<u>X (1-2 hours)+ CT</u>	X <u>(+/-30 mins)</u>		<u>X</u> <u>(end of dose to 2hrs)</u> <u>cumulative collection^a</u>
<u>4 hours</u> <u>(+/- 30 mins)</u>			X	X	
<u>24 hours</u>	<u>X^c (18-26 hours)</u>	<u>X (18-26 hours)</u>	X (+/- 2 hr)	X (+/- 2 hr)	X (+/- 2 hr)
<u>48 hours</u>	<u>X (36-48 hours)</u>	<u>X (36-48 hours)</u>	X (+/- 2 hr)		X (+/- 2 hr)
<u>72 hours</u>			X (+/- 2 hr)		X (+/- 2 hr)
<u>Day 6</u>			X		
<u>156-168 hours</u>	X	X			

^a Whole urine collection required between end of infusion and 2hrs post infusion, before the first image

^b Intense ECG monitoring required on day 1 cycle 1 only. Predose (Typically the patient lies supine at least 30 minutes prior to dosing. The triplicate ECGs are collected at approximately 1.5-2 min intervals during the last 5 minutes of the 30 minutes. The next triplicate is collected 1hr post dose, typically the patient is supine for 15 minutes (45 minutes post dose) and 3 readings are taken in last 5 minutes. The next triplicate is at 4hrs and the final at 24hrs and patient is supine resting for 15 minutes - after 10 minutes take 3 readings. ECG monitoring should be performed prior to blood collection.)

^c After urine collection

BP to be collect prior to each ECG

Page 115 of 115

3.5 Measurements, Recording, Calculation and Analysis of Sub-study Data

Details regarding the methods used to measure, record and perform necessary calculations of the data acquired can be found in the sub-study manual.

Protocol no. PSMA-617-01
Version no.: 3.0
DE

Endocyte, Inc.
01 April 4.1
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 4.1 DE

Date: 09 August 2019

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617

Sponsor: Endocyte, Inc.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Page 2 of 103

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Table of Contents

Site Principal Investigator Signature	2
Table of Contents.....	3
Revision History	8
Clinical Trial Summary.....	10
List of Abbreviations and Definitions	13
1. Introduction	15
1.1 Background information	15
1.2 Summary of nonclinical studies with clinical significance.....	19
1.3 Summary of known and potential risks and benefits	20
2. Trial Objectives and Endpoints	21
2.1 Trial objectives.....	21
2.1.1 Primary objective	21
2.1.2 Key secondary objectives.....	21
2.1.3 Additional secondary objectives	21
2.2 Trial endpoints	21
2.2.1 Alternate Primary endpoint	21
2.2.2 Key Secondary endpoints	22
2.2.3 Additional Secondary endpoints	22
3. Trial Design.....	23
3.1 Overview of the clinical trial design.....	23
3.1.1 Study design update.....	26
3.1.2 Study design update - Dosimetry, PK and ECG sub-study	26
3.2 Rationale for the study design.....	27
3.3 Measures taken to minimize/avoid bias	27
3.4 Description of the clinical trial	27
3.4.1 Description of investigational medicinal product.....	27
3.4.2 Dosage and rationale for dose selection	27
3.4.3 Subject allocation to treatment	28
3.4.4 End of treatment visit	29
3.4.5 Duration of Subject Participation	29
3.5 End of trial definition.....	29
4. Selection and discontinuation of Subjects.....	29
4.1 Inclusion criteria	30
4.2 Exclusion criteria	31

4.3	Subject withdrawal of consent for study or treatment	32
5.	Treatment of Subjects	33
5.1	Treatment with the investigational medicinal product.....	33
5.1.1	Administration of ⁶⁸ Ga-PSMA-11.....	33
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-617	33
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	33
5.1.4	Management of toxicity adverse events: dosing delays and modification	34
5.2	Best supportive/best standard of care.....	36
5.3	Concomitant medications/ supportive care	37
5.3.1	Permitted concomitant medications/ supportive care.....	37
5.3.2	Prohibited concomitant medications	37
5.4	Monitoring treatment compliance	37
5.5	Treatment discontinuation	37
6.	Study Assessments and Procedures	38
6.1	Screening procedures and baseline assessments	38
6.2	Efficacy assessments.....	40
6.2.1	Radiographic imaging for tumor assessments	40
6.2.2	Additional Imaging Analyses	40
6.2.3	RECIST criteria.....	41
6.2.4	Symptomatic skeletal events	41
6.2.5	Pain score	41
6.2.6	Health-related quality of life	41
6.2.7	Health Economics.....	42
6.2.8	Clinical progression.....	43
6.2.9	PSA levels	43
6.3	Safety assessments	43
6.3.1	Clinical laboratory evaluations	43
6.3.2	Vital signs	44
6.3.3	Electrocardiograms	44
6.3.4	Birth Control	44
6.4	End of treatment visit procedures	44
6.5	Long-term follow-up procedures	44
7.	Adverse Events	45
7.1	Adverse event definitions	45
7.2	Evaluating and recording adverse events	46
7.3	Immediate Adverse Event Reporting	46

7.3.1	Serious Adverse Events.....	46
7.3.2	Serious adverse event subject follow-up	47
7.3.3	Sponsor Contact Information for Immediate Reporting.....	47
8.	Statistics	47
8.1	Revision to the protocol and statistical analyses of rPFS and OS.....	47
8.2	Revisions to planned analyses	48
8.3	Sample size and power determination	48
8.4	Analysis populations.....	49
8.5	Demographics and baseline disease characteristics	49
8.6	Patient disposition.....	50
8.7	Efficacy analyses	50
8.7.1	Alternate primary endpoint analysis.....	50
8.7.2	Secondary efficacy analyses.....	51
8.8	Safety analyses.....	53
8.8.1	Extent of exposure.....	53
8.8.2	Analysis of adverse events	53
8.8.3	Analysis of laboratory assessments.....	53
8.8.4	Analysis of vital sign data	54
8.9	IDMC and interim data evaluation	54
8.9.1	IDMC	54
8.9.2	Formal interim analysis of OS	54
9.	Access to Source Data/Documents	54
10.	Ethics.....	55
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	55
10.2	Informed consent	55
10.3	Health Insurance Portability and Accountability Act.....	55
10.4	Confidentiality.....	56
11.	Compliance and quality control	56
11.1	Compliance with Monitoring and Audits	56
12.	Data Handling, Record Keeping, and Compliance	57
12.1	Investigational medicinal product accountability.....	57
12.2	Breaking the blind	57
12.3	Data collection forms and source document identification	57
12.4	Record maintenance and retention	58
12.5	Archiving	58

13. Publication Policy.....	58
14. References	59
Appendix 1 Schedules of Assessments	66
Appendix 2 Suggested treatment guidelines	74
Appendix 3 Principal investigator signature	75
Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	76
Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	77
Appendix 5 Common Terminology Criteria for Adverse Events	78
Appendix 6 Response Evaluation Criteria in Solid Tumors	79
Appendix 7 Prostate Cancer Working Group 3 Recommendations.....	80
Appendix 8 BPI-SF (<i>sample only, not for patient use</i>).....	82
Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	85
Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (<i>sample only, not for patient use</i>)	89
Appendix 11 PCCTC Bone Scan Assessment Tool.....	93
Appendix 12 Dosimetry, PK and ECG Sub- study	99
1. DOSIMETRY, PK and ECG SUB-STUDY DESIGN.....	99
2. Objectives.....	99
2.1 Primary Objective:	99
2.2 Secondary Objectives:	99
3. DOSIMETRY, PK and ECG SUB-STUDY ASSESSMENTS	99
3.1 Imaging Assessments.....	100
3.1.1 Equipment	100
3.2 PK Blood Sampling	100
3.3 Cardiac Assessments.....	101
3.4 Urine	101
3.5 Measurements, Recording, Calculation and Analysis of Sub-study Data	103

List of tables

Table 1 Toxicity management and dose modification recommendations	34
Table 2 Screening procedures and baseline assessments	38

Table 3	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)	67
Table 4	Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....	69
Table 5	Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) - (Not applicable for V4.1 DE)	71
Table 6	Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) - (Not applicable for V4.1 DE)	72
List of figures		
Figure 1	Diagram of trial design.....	24

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added. <p>Updated reference section</p>
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.• Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%)

		<p>and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.</p> <ul style="list-style-type: none">• Additional imaging analyses details were added for study ^{68}Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.• Further clarification on the start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.• Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression.
4.1	09 August 2019	<p>DE amendment - all protocol changes noted above for Versions 2, 3 and 4 are also included in DE amendment 4.1</p> <p>Added a dosimetry, pharmacokinetics (PK) and electrocardiogram (ECG) sub-study which will include a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients from selected sites in Germany. Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.</p>

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory - Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.• Dosimetry, PK and ECG in a sub-study of approximately 30 patients
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</p> <p>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up. A long-term follow-up period will include the collection of rPFS survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (± 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs). These patients will be asked to sign a separate consent detailing what kind of long term follow up</p>

	<p>assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 814 patients.</p> <p>A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617.</p> <p>In order to not bias the results obtained from randomized patients in the main study, the data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The sub-study details and analyses will be presented in a separate report.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4. Patients included in the sub-study will receive the investigation arm (^{177}Lu -PSMA-617 plus best supportive/best standard of care).
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6

	(i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (± 1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management of patients in the sub-study will remain identical to that implemented in the main study.
Statistical methodology:	Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5 th , 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5 th , 2019). Following the analysis of rPFS and the interim analysis of OS, a final analysis of OS will be performed when 508 death events have accrued and the alpha level applied will be 0.02 1-sided. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.
Duration of Study:	Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BfS	Federal Office for Radiation Protection (Bundesamt für Strahlenschutz)
BPI-SF	Brief Pain Inventory - Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DE	Germany
DOR	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQoL) - 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPLC	High pressure liquid chromatography
HR	Hazard ratio
hr	hour
HRQoL	Health-related quality of life
IB	Investigator's Brochure

Abbreviation	Term/Definition
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
Min(s)	Minute(s)
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SPEC	Single-photon emission computed tomography
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol. The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease ([Ferlay et al 2013](#), [Bray et al 2012](#)).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men ([Siegel et al 2017](#)), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednison in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months ([Smith et al 2016](#)). Post-docetaxel mCRPC patients have an annual death rate of 73% ([Scher et al 2015](#)).

The median age at diagnosis of mCRPC is 70 years ([Flaig et al 2016](#)). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases ([Kirby et al 2011](#)), and 49% of them will develop a serious skeletal event within 2 years ([Saad et al 2004](#)). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being ([Weinfurt et al 2005](#)). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral

disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life ([Cella et al 2009](#)). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal ([Zielinski et al 2014](#)).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months ([Azad et al 2015](#), [Cheng et al 2015](#), [Badrising et al 2014](#), [Brasso et al 2015](#), [Loriot et al 2013](#), [Noonan et al 2013](#)). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands ([Bostwick et al 1998](#), [Ghosh and Heston 2004](#), [Mannweiler et al 2009](#)). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease ([Ross et al 2003](#)). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium-energy β -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile

and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of \geq 6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the overall response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ^{177}Lu -PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1–2, of ^{177}Lu -PSMA-617 treatment are dry mouth, nausea, vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible

hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface area of 1.7 m².

However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu -PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ^{177}Lu -PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG (sub-study of approximately 30 patients).

2.2 Trial endpoints

2.2.1 Alternate Primary endpoint

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression

- Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
 - c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
 6. Dosimetry, PK, and ECG in a sub-study of approximately 30 patients

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

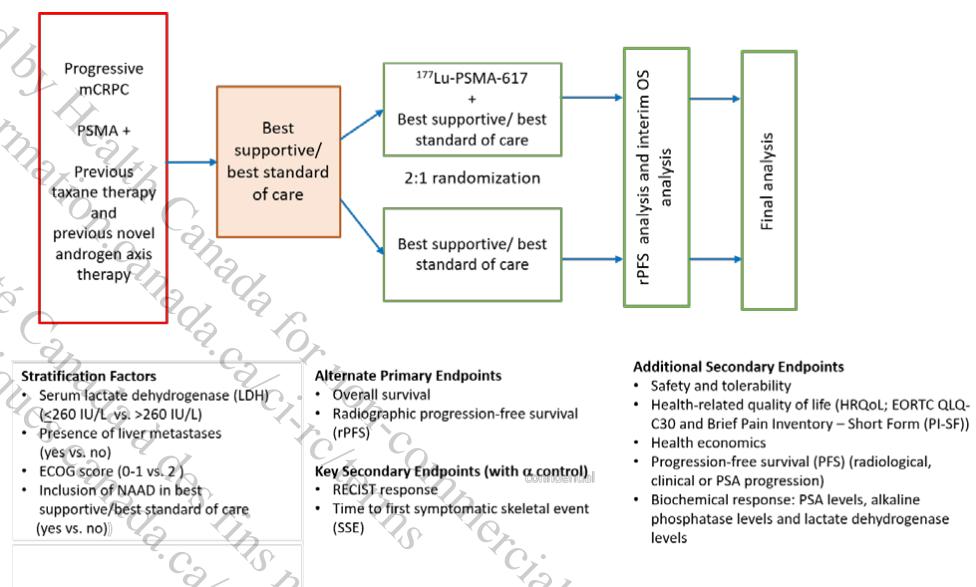


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

Page 26 of 103

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.1.2 Study design update – Dosimetry, PK and ECG sub-study

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

In order to not bias the results obtained from randomized patients in the main study, the data of the substudy patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The substudy details and analyses will be presented in a separate report. Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific tests conducted in the sub-study, as described in Appendix 12, and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms, with exception to the additional 30 patients in the sub-study who will receive the investigational treatment. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu -PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu -PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu -PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu -PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu -PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu -PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu -PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Patients included in the sub-study will not undergo randomization as all patients will receive the investigational arm.

Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

It is anticipated that it will take approximately 14 months to randomize the required 814 patients in the study. After the last patient is randomized, patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga -PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation or intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesion(s) by bone scan (2+2 PCWG3 criteria, [Scher et al 2016](#)).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

a. Bone marrow reserve:

- White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
- Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
- Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

b. Hepatic:

- Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

c. Renal:

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$

15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L).

16. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible.

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 3 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:

- Are allowed by the protocol.
- Have been agreed to by the treating investigator and patient.
- Allow for the management of the patient without $^{177}\text{Lu-PSMA-617}$.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the treatment arm in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to

these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga -PSMA-11

For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure. The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(\pm 5) minutes before and at 30(\pm 5) and 60(\pm 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ¹⁷⁷Lu-PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ¹⁷⁷Lu-PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ¹⁷⁷Lu-PSMA-617. At the discretion of the investigator, a dose of ¹⁷⁷Lu-PSMA-617 may be delayed or reduced. **Table 1** provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ¹⁷⁷Lu-PSMA-617 must be discontinued. Once a dose is reduced, treatment with ¹⁷⁷Lu-PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ¹⁷⁷Lu-PSMA-617 must be discontinued. If treatment with ¹⁷⁷Lu-PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count <3.0 \times 10⁹/L• ANC <1.5 \times 10⁹/L	\geq Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematologic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Thrombocytopenia (platelet count of < 75 x 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
-------	-------	----------------------------

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, or other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ^{177}Lu -PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization (enrollment for sub-study patients) except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Adverse Event (AE) monitoring and Serious Adverse Event (SAE) reporting	Begins at time of consent.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu -PSMA-617 within 28 days after randomization.

^a For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#). The timing of the additional assessments for the sub-study are provided in [Appendix 12](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ^{68}Ga -PSMA-11 scan data will be used for additional exploratory analyses. The ^{68}Ga -PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ^{68}Ga -PSMA-11 PET/CT scans by

assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ⁶⁸Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ⁶⁸Ga-PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.5 Pain score

Pain will be assessed using the BPI-SF.

The BPI-SF will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort,

anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993, Esper et al 1997](#))
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) analysis will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

- | | | | |
|------------|--|--|---|
| Chemistry | <ul style="list-style-type: none">• sodium• potassium• total and direct bilirubin• ALP• AST• ALT | <ul style="list-style-type: none">• LDH• blood urea nitrogen• creatinine• uric acid• phosphorus• chloride | <ul style="list-style-type: none">• bicarbonate• calcium• glucose• total protein• albumin |
| Urinalysis | <ul style="list-style-type: none">• urine pH• protein content• specific gravity• appearance and color | <ul style="list-style-type: none">• glucose• ketones | |
| Hematology | <ul style="list-style-type: none">• complete blood count (white blood cell count and differential)• red blood cell count• hemoglobin• hematocrit• platelet count | | |

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g., condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 3 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission

to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death;• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ^{68}Ga -PSMA-11 and/or ^{177}Lu -PSMA-617; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of

the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non- confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341

deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p < 0.004$ 1-sided is achieved for rPFS and $p < 0.001$ 1-sided, is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p < 0.004$ 1-sided is achieved for rPFS but $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS but $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS and $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p < 0.020$ to $p < 0.025$ in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard

Page 50 of 103

deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. PFS eventsThe primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, stratified for the randomization stratification factors.

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to

occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is **not required** to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level **or** OS to meet its allocated alpha level at **either** (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) **or** (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval

and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG in a sub-study of approximately 30 patients presented separately from the main study analyses.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value. DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set. The same analyses will be performed separately in the sub-study of approximately 30 patients.

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ⁶⁸Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ⁶⁸Ga-PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ⁶⁸Ga-PSMA-11 dosing up to 6 days after the date of ⁶⁸Ga-PSMA-11 dosing as long as prior to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ⁶⁸Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ⁶⁸Ga-PSMA-11 TEAEs. Unrelated ⁶⁸Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

AEs leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and interim data evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal interim analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

Page 55 of 103

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of

Page 56 of 103

the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are

requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015; 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Page 60 of 103

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2019;37(suppl 7S): 228. Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract.* 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research.* 2018 Jul;78(13): CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(6):987–88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of Oncology* 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Page 63 of 103

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013;24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXNN Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate

Page 64 of 103

resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 65 of 103

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ¹⁷⁷Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [¹⁷⁷Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017; DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 66 of 103

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X-----					X-----
AE monitoring ^a	X-----					X-----
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X-----					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01
Version no.: 4.1 DE

Endocyte, Inc.
09 August 2019
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^e					X ^a	X ^a	X	
AE monitoring ^b	X ^e					X ^a	X ^a	X	
Weight	X ^e						X ^c	X	
ECOG	X ^e						X ^c	X	
Directed physical exam	X ^e						X ^c	X	
Vital signs ^d	X ^e						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{g,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^e		X ^e		X ^e		X ^c	X	
Chemistry ^f	X ^e		X ^e		X ^e		X ^c	X	
Serum testosterone	X ^e						X ^c	X	
PSA	X ^e						X ^c	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

* After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

Protocol no. PSMA-617-01
Version no. 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

^{**} Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards. ^a Phone evaluation is allowed but are not required for visits after Day 1 of each cycle.

^b Adverse event monitoring will commence at time of consent. .

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ¹⁷⁷Lu-PSMA-617 administration.

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (\pm 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician, or site research team member.

AE = adverse event; ANC= absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell.

Table 5. Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) – (Not applicable for V4.1 DE)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: Up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will begin at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01
Version no. 4.1 DE

Endocyte, Inc.
09 August 2019

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) – (Not applicable for V4.1 DE)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Cycle Week:							Every 12 weeks (\pm 4 days)		Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^a					X ^a		X	
AE monitoring ^b	X ^a					X ^a		X	
Weight	X ^c						X ^b	X	
ECOG	X ^c						X ^b	X	
Directed physical exam	X ^c						X ^b	X	
Vital signs ^c	X ^c						X ^b	X	
EQ-5D-5L	X ^{e,h}						X ^{d,g}	X ^{d,g}	
FACT-P	X ^{e,h}						X ^{d,g}	X ^{d,g}	
BPI-SF	X ^{e,h}						X ^{d,g}	X	
Best supportive/best standard of care	As per physician's orders								
Hematology ^e	X ^c		X ^b		X ^b		X ^b	X	
Chemistry ^e	X ^c		X ^b		X ^b		X ^b	X	
Serum testosterone	X ^c						X ^b	X	
PSA	X ^c						X ^b	X	
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)								

^{**} Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

Protocol no. PSMA-617-01
Version no. 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

- ^a Phone evaluation are allowed but are not required for visits after Day 1 of each cycle. .
- ^b Adverse event monitoring will commence at time of consent.
- ^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.
- ^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).
- ^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.
- ^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).
- ^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.
- ^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Appendix 3 Principal investigator signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramidate. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 78 of 103

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Page 79 of 103

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none"> Record outcome as new lesions, no new lesions or resolved lesion First scheduled reassessment: <ul style="list-style-type: none"> No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: <ul style="list-style-type: none"> No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: <ul style="list-style-type: none"> No new lesions: continue New lesions: progression Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none"> Exclude pseudoprogression in the absence of symptoms or other signs of progression At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule) If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan Date of progression is the date of the scan that first documents the second lesion Changes in intensity of uptake alone do not constitute either progression or regression Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none"> Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to [Scher et al 2016](#) for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 82 of 103

Appendix 8 BPI-SF (*sample only, not for patient use*)

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Page 83 of 103

Brief Pain Inventory (Short Form)

Time: ___ : ___ AM PM

Today's Date (day, month, year):

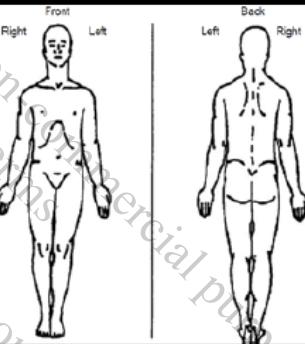
JAN	<input type="checkbox"/>	JAN	<input type="checkbox"/>	MAR	<input type="checkbox"/>	MAY	<input type="checkbox"/>	JUL	<input type="checkbox"/>	SEP	<input type="checkbox"/>	NOV	<input type="checkbox"/>
Day	-	FEB	<input type="checkbox"/>	APR	<input type="checkbox"/>	JUN	<input type="checkbox"/>	AUG	<input type="checkbox"/>	OCT	<input type="checkbox"/>	DEC	-
													Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

A horizontal scale with numerical labels 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. Above the scale, there is a handwritten note: "Pain as bad as you can imagine".

Copyright 1991 Charles S. Cleland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Today's Date (Day, Month, Year): <u> </u> - <u> </u> - <u> </u> (Example: 08-FEB-2016) <u> </u> DAY <u> </u> MONTH <u> </u> YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Page 86 of 103



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

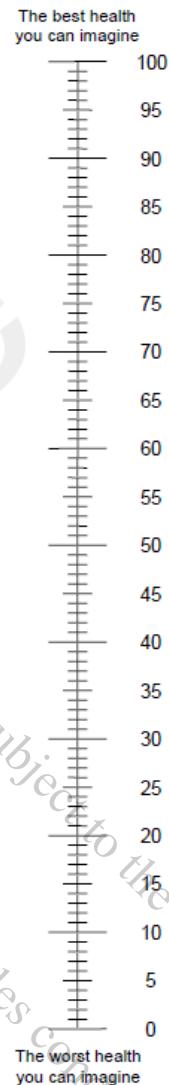
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

Page 88 of 103

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

Page 89 of 103

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy –
Prostate) (*sample only, not for patient use*)**

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

- GE1
GE2
GE3
GE4
GE5
GE6

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness.....	0	1	2	3	4
I am losing hope in the fight against my illness.....	0	1	2	3	4
I feel nervous.....	0	1	2	3	4
I worry about dying.....	0	1	2	3	4
I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

- GF1
GF2
GF3
GF4
GF5
GF6
GF7

	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling.....	0	1	2	3	4
I am able to enjoy life.....	0	1	2	3	4
I have accepted my illness.....	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun.....	0	1	2	3	4
I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERN	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 93 of 103

Appendix 11 PCCTC Bone Scan Assessment Tool

Protocol no. PSMA-617-01
Version no.: 4.1 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

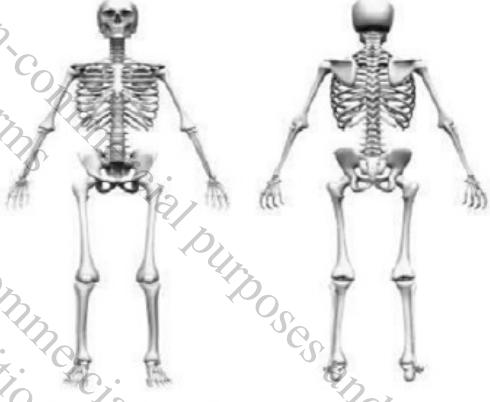
Endocyte, Inc.
09 August 2019

Page 94 of 103

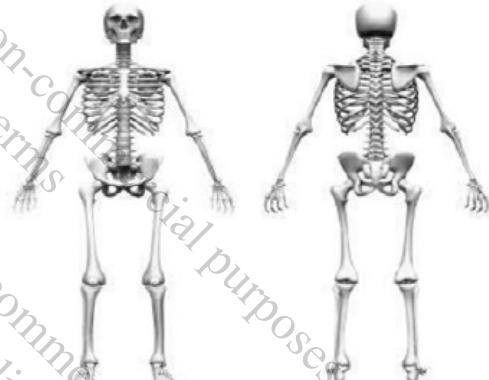
Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 8 BASELINE Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening:	Draw site(s) of NEW lesion(s) on skeleton:  <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
* Presence of new lesions at this time does not confirm progression	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan:	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

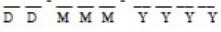
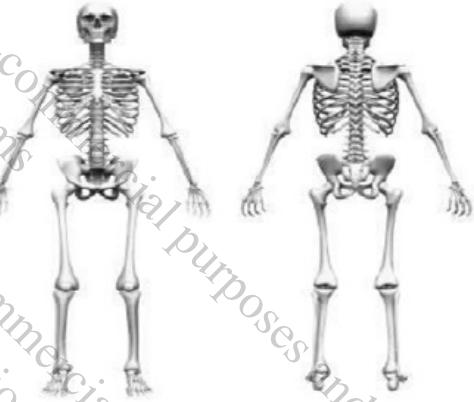
Page 97 of 103

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton:
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 98 of 103

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

APPENDIX 12 DOSIMETRY, PK AND ECG SUB-STUDY

1. DOSIMETRY, PK AND ECG SUB-STUDY DESIGN

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study.

Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific assessments conducted in the sub-study, as described below and the separate sub-study manual, the treatment regimen and patient care management will be identical to that implemented in the main study.

The results of this sub-study will be included in a Dosimetry Study Report addendum that will accompany the main study report.

2. OBJECTIVES

To evaluate dosimetry, pharmacokinetics, and ECG.

2.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ¹⁷⁷Lu-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney and bone marrow)

2.2 Secondary Objectives:

- Define the pharmacokinetic profile of ¹⁷⁷Lu-PSMA-617;
- Evaluate ECGs during treatment with ¹⁷⁷Lu-PSMA-617;
- Evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617;
- Evaluate the metabolic stability of ¹⁷⁷Lu-PSMA-617

3. DOSIMETRY, PK AND ECG SUB-STUDY ASSESSMENTS

The sub-study patients will require full body (planar) and 3D SPECT/CT imaging, blood PK sampling and ECGs, during cycle 1 of treatment. Urine will be collected for HPLC (High-performance liquid chromatography) analysis.

Refer to Table 7 and the sub-study manual for timing assessments.

3.1 Imaging Assessments

Baseline images will be used to determine volumes in regions of interest in selected major source organs such as the liver, spleen and kidneys. Refer to the sub-study manual for further details on measurements and calculations.

Serial gamma camera images (whole body planar images) will be obtained in the first treatment cycle detailed in table 7 below. 3D SPECT/CT scans will be also performed in the upper abdomen (comprising kidneys, liver and spleen).

Full body planar images will be acquired at the following time points after administration:

- 1-2 hours
- 18-26 hours
- 36-48 hours
- 156-168 hours

3D SPECT images will be acquired at the following time points after administration:

- 1-2 hours (Additional CT imaging required)
- 18-26 hours
- 36-48 hours
- 156-168 hours

3.1.1 Equipment

The following equipment will be required:

1. A gamma-camera with medium energy collimator.
2. A Co-57 flood source or a Lu-177 or Tc-99m filled flood source for the transmission scan. Well counter with multichannel analyzer or gamma counter to determine ¹⁷⁷Lu radioactivity in blood and urine samples.
3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.

3.2 PK Blood Sampling

Blood PK samples will be collected during cycle 1 of the treatment, to provide data for bone marrow radiation dose calculations and for PK assessment.

At cycle 1, blood samples (1mL) will be collected in heparinized tubes starting immediately before the start of administration, end of administration, then approximately 20mins (+/- 5mins), 60mins(+/- 5mins), 2hr (+/- 30mins), 4hr (+/- 30mins), 24hr (+/- 2hrs), 48hr (+/- 2hrs), 72hr (+/-

2hrs) & day 6 post end of infusion. Blood PK samples should be collected after ECGs, where timepoints overlap. Refer to Table 7 for the timing of assessments.

Radioactivity in blood will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time points have to be recorded by site. The exact time point of each measurement and the calibration factor must be documented by the investigational site.

3.3 Cardiac Assessments

A twelve-lead ECG test will be performed in triplicate for all patients during Cycle 1 of treatment for up to 4 time points (pre-administration and thereafter at approximately 1hr, 4hrs and 24hrs post treatment). Blood Pressure (BP) should be measured prior to each ECG time point.

Patients should have a light breakfast on the morning of treatment.

In the event of a clinically significant finding (i.e., QTcF increase from baseline of >30ms occurs), an additional single safety ECG should be repeated prior to dosing at cycle 2.

All pre-medications will be administered during the time interval ranging from 90 mins to 60 mins before the start of infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen.

If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1hr before the start of infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1hr before, until 8hr after the start of infusion, unless clinically required.

Data obtained will be analyzed by a central reader to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Clinically significant abnormalities will be recorded on the Adverse Event page of the eCRF.

ECG parameters will include HR, RR interval, PR interval, QRS interval and QT interval. QT intervals will be corrected for HR.

3.4 Urine

Total urine excreted will be collected between the end of infusion and the time of the first image (2hrs post infusion).

The extent of elimination of the radiolabeled compound must be determined before acquiring the first image. Therefore, the urine eliminated between the infusion and the time of the first image must be collected quantitatively (possibly in one single container), the whole volume or mass of this excreted urine must be measured and 1 mL sample withdrawn for radioactivity measurement. Radioactivity in urine will be measured at the investigational site, with a properly

calibrated gamma counter or similar system. The exact time point of urine collection and measurement, as well as the calibration factor must be documented by the investigational site.

An aliquot (10 mL) of the whole urine collected between the infusion and the time of the first image will be also sent to a central laboratory for HPLC analysis. Moreover, for HPLC analysis purpose only, additional urine samples (around 10 mL, no need to have cumulative urine samples for this assessment) will be collected from the patients at 24hrs (+/-2hrs), 48hrs (+/-2hrs) and 72hrs (+/-2hrs). Collected samples will be sent to a central laboratory for analysis by HPLC according to a validated procedure, in order to determine the elimination of the radioactive compound and possible metabolites, if any, over time.

Table 7: Sub-Study Assessment timepoints (Cycle 1 only)

	Planar full body imaging	3D SPECT imaging	Blood sampling	BP & Intense ECG ^{b,d}	Urine
Pre dose			X	X	
End of dose			X		
20 mins (+/- 5 mins)			X		X (end of dose to 2hrs)
60 mins (+/- 5 mins)			X	X	cumulative collection ^a
2 hours	X (1-2 hours) ^c	X (1-2 hours)+ CT	X (+/-30 mins)		
4 hours (+/- 30 mins)			X	X	
24 hours	X ^c (18-26 hours)	X (18-26 hours)	X (+/- hr)	X (+/- hr)	X (+/- hr)
48 hours	X (36-48 hours)	X (36-48 hours)	X (+/- hr)		X (+/- hr)
72 hours			X (+/- hr)		X (+/- hr)
Day 6			X		
156-168 hours	X	X			

^a Whole urine collection required between end of infusion and 2hrs post infusion, before the first image

^b Intense ECG monitoring required on day 1 cycle 1 only. Predose (Typically the patient lies supine at least 30 minutes prior to dosing. The triplicate ECGs are collected at approximately 1.5-2 min intervals during the last 5 minutes of the 30 minutes. The next triplicate is collected 1hr post dose, typically the patient is supine for 15 minutes (45 minutes post dose) and 3 readings are taken in last 5 minutes. The next triplicate is at 4hrs and the final at 24hrs and patient is supine resting for 15 minutes - after 10 minutes take 3 readings. ECG monitoring should be performed prior to blood collection.

^c After urine collection

BP to be collect prior to each ECG

Page 103 of 103

3.5 Measurements, Recording, Calculation and Analysis of Sub-study Data

Details regarding the methods used to measure, record and perform necessary calculations of the data acquired can be found in the sub-study manual.



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 4.14 DE

Date: 09 August 2019 22 July 2020

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617

Sponsor: Endocyte, Inc.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Page 2 of 103

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

|
Protocol no. PSMA-617-01
Version no.: 4.~~44~~ DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019 22 July 2020

Table of Contents

Site Principal Investigator Signature	2
Table of Contents.....	3
Revision History	8
Clinical Trial Summary.....	10
List of Abbreviations and Definitions	13
1. Introduction	15
1.1 Background information.....	15
1.2 Summary of nonclinical studies with clinical significance.....	19
1.3 Summary of known and potential risks and benefits	20
2. Trial Objectives and Endpoints	21
2.1 Trial objectives.....	21
2.1.1 Primary objective	21
2.1.2 Key secondary objectives.....	21
2.1.3 Additional secondary objectives	21
2.2 Trial endpoints	21
2.2.1 Alternate Primary endpoint	21
2.2.2 Key Secondary endpoints	22
2.2.3 Additional Secondary endpoints	22
3. Trial Design.....	23
3.1 Overview of the clinical trial design.....	23
3.1.1 Study design update.....	26
3.1.2 Study design update - Dosimetry, PK and ECG sub-study	26
3.2 Rationale for the study design.....	27
3.3 Measures taken to minimize/avoid bias	27
3.4 Description of the clinical trial	27
3.4.1 Description of investigational medicinal product.....	27
3.4.2 Dosage and rationale for dose selection	27
3.4.3 Subject allocation to treatment	28
3.4.4 End of treatment visit	29
3.4.5 Duration of Subject Participation	29
3.5 End of trial definition.....	29
4. Selection and discontinuation of Subjects.....	29
4.1 Inclusion criteria	30
4.2 Exclusion criteria	31

4.3	Subject withdrawal of consent for study or treatment32
5.	Treatment of Subjects33
5.1	Treatment with the investigational medicinal product.....	.33
5.1.1	Administration of ⁶⁸ Ga-PSMA-11.....	.33
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-61733
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections33
5.1.4	Management of toxicity adverse events: dosing delays and modification34
5.2	Best supportive/best standard of care.....	.36
5.3	Concomitant medications/ supportive care37
5.3.1	Permitted concomitant medications/ supportive care.....	.37
5.3.2	Prohibited concomitant medications37
5.4	Monitoring treatment compliance37
5.5	Treatment discontinuation37
6.	Study Assessments and Procedures38
6.1	Screening procedures and baseline assessments38
6.2	Efficacy assessments.....	.40
6.2.1	Radiographic imaging for tumor assessments40
6.2.2	Additional Imaging Analyses40
6.2.3	RECIST criteria.....	.41
6.2.4	Symptomatic skeletal events41
6.2.5	Pain score41
6.2.6	Health-related quality of life41
6.2.7	Health Economics.....	.42
6.2.8	Clinical progression.....	.43
6.2.9	PSA levels43
6.3	Safety assessments43
6.3.1	Clinical laboratory evaluations43
6.3.2	Vital signs44
6.3.3	Electrocardiograms44
6.3.4	Birth Control44
6.4	End of treatment visit procedures44
6.5	Long-term follow-up procedures44
7.	Adverse Events45
7.1	Adverse event definitions45
7.2	Evaluating and recording adverse events.....	.46
7.3	Immediate Adverse Event Reporting46

7.3.1	Serious Adverse Events.....	46
7.3.2	Serious adverse event subject follow-up	47
7.3.3	Sponsor Contact Information for Immediate Reporting.....	47
8.	Statistics.....	47
8.1	Revision to the protocol and statistical analyses of rPFS and OS.....	47
8.2	Revisions to planned analyses	48
8.3	Sample size and power determination	48
8.4	Analysis populations.....	49
8.5	Demographics and baseline disease characteristics	49
8.6	Patient disposition.....	50
8.7	Efficacy analyses	50
8.7.1	Alternate primary endpoint analysis.....	50
8.7.2	Secondary efficacy analyses.....	51
8.8	Safety analyses.....	53
8.8.1	Extent of exposure.....	53
8.8.2	Analysis of adverse events	53
8.8.3	Analysis of laboratory assessments	53
8.8.4	Analysis of vital sign data	54
8.9	IDMC and interim data evaluation	54
8.9.1	IDMC	54
8.9.2	Formal interim analysis of OS	54
9.	Access to Source Data/Documents	54
10.	Ethics.....	55
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	55
10.2	Informed consent	55
10.3	Health Insurance Portability and Accountability Act	55
10.4	Confidentiality	56
11.	Compliance and quality control	56
11.1	Compliance with Monitoring and Audits.....	56
12.	Data Handling, Record Keeping, and Compliance	57
12.1	Investigational medicinal product accountability	57
12.2	Breaking the blind.....	57
12.3	Data collection forms and source document identification.....	57
12.4	Record maintenance and retention.....	58
12.5	Archiving	58

13. Publication Policy58
14. References59
Appendix 1 Schedules of Assessments.....	.66
Appendix 2 Suggested treatment guidelines.....	.74
Appendix 3 Principal investigator signature.....	.75
Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison76
Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison77
Appendix 5 Common Terminology Criteria for Adverse Events.....	.78
Appendix 6 Response Evaluation Criteria in Solid Tumors.....	.79
Appendix 7 Prostate Cancer Working Group 3 Recommendations80
Appendix 8 BPI-SF (<i>sample only, not for patient use</i>).....	.82
Appendix 9 EQ-5D-5L (European Quality of Life (EuroQoL) - 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)85
Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (<i>sample only, not for patient use</i>)89
Appendix 11 PCCTC Bone Scan Assessment Tool93
Appendix 12 Dosimetry, PK and ECG Sub- study99
1. DOSIMETRY, PK and ECG SUB-STUDY DESIGN99
2. <u>Amendment 4.4 RATIONALE</u>99
3. Objectives.....	.99
3.1 Primary Objective:99
3.2 Secondary Objectives:99
4. DOSIMETRY, PK and ECG SUB-STUDY ASSESSMENTS	100
4.1 Imaging Assessments.....	100
4.1.1 Equipment	100
4.2 PK Blood Sampling	101
4.3 Cardiac Assessments.....	101
4.4 Urine	102
4.5 <u>Renal Function Surveillance</u>	102
4.6 Measurements, Recording, Calculation and Analysis of Sub-study Data.....	103

List of tables

Table 1 Toxicity management and dose modification recommendations	34
---	----

Protocol no. PSMA-617-01
Version no.: 4.44 DE

Endocyte, Inc.
09-August-2019 22 July 2020

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 2 Screening procedures and baseline assessments.....	38
Table 3 Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)	67
Table 4 Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)	69
Table 5 Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) - (Not applicable for V4.4 DE)	71
Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) - (Not applicable for V4.4 DE).....	72
Table 7 Sub-Study Assessment time points.....	102
List of figures	
Figure 1 Diagram of trial design.....	24

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added. <p>Updated reference section</p>
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.• Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%)

		<p>and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.</p> <ul style="list-style-type: none">• Additional imaging analyses details were added for study ^{68}Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.• Further clarification on the start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.• Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression.
4.1	09 August 2019	<p>DE amendment - all protocol changes noted above for Versions 2, 3 and 4 are also included in DE amendment 4.1</p> <p>Added a dosimetry, pharmacokinetics (PK) and electrocardiogram (ECG) sub-study which will include a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients from selected sites in Germany. Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.</p>
<u>4.4 DE</u>	<u>22 July 2020</u>	<p><u>DE amendment - all modifications for Version 4.4 DE pertain to the Dosimetry sub-study and accordingly are included in Appendix 12 of this document.</u></p> <ul style="list-style-type: none">• <u>Additional imaging procedures of whole body planar and 3D SPECT from cycle 2 through cycle 6 of PSMA-617 treatment to align and comply with local radioprotection laws and established guidelines in Germany.</u>• <u>Implementation of estimated glomerular filtration rate (eGFR) from cycle 1 through cycle 6 of PSMA-617 treatment to further assess potential renal toxicity.</u>

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory - Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.• Dosimetry, PK and ECG in a sub-study of approximately 30 patients
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</p> <p>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up. A long-term follow-up period will include the collection of rPFS survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (± 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs). These patients will be asked to sign a separate consent detailing what kind of long term follow up</p>

	<p>assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 814 patients.</p> <p>A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617.</p> <p>In order to not bias the results obtained from randomized patients in the main study, the data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The sub-study details and analyses will be presented in a separate report.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4. Patients included in the sub-study will receive the investigation arm (^{177}Lu -PSMA-617 plus best supportive/best standard of care).
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6

(i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (± 1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs.
Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management of patients in the sub-study will remain identical to that implemented in the main study.
Statistical methodology: Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5 th , 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5 th , 2019). Following the analysis of rPFS and the interim analysis of OS, a final analysis of OS will be performed when 508 death events have accrued and the alpha level applied will be 0.02 1-sided. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.
Duration of Study: Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BfS	Federal Office for Radiation Protection (Bundesamt für Strahlenschutz)
BPI-SF	Brief Pain Inventory - Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DE	Germany
DOR	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQol) - 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy - Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPLC	High pressure liquid chromatography
HR	Hazard ratio
hr	hour
HRQoL	Health-related quality of life
IB	Investigator's Brochure

Abbreviation	Term/Definition
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
Min(s)	Minute(s)
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SPEC	Single-photon emission computed tomography
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol. The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease ([Ferlay et al 2013](#), [Bray et al 2012](#)).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men ([Siegel et al 2017](#)), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months ([Smith et al 2016](#)). Post-docetaxel mCRPC patients have an annual death rate of 73% ([Scher et al 2015](#)).

The median age at diagnosis of mCRPC is 70 years ([Flaig et al 2016](#)). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases ([Kirby et al 2011](#)),([Kirby et al 2011](#)), and 49% of them will develop a serious skeletal event within 2 years ([Saad et al 2004](#)). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being ([Weinfurt et al 2005](#)). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral

disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life (Cella et al 2009). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal (Zielinski et al 2014).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months (Azad et al 2015, Cheng et al 2015, Badrising et al 2014, Brasso et al 2015, Loriot et al 2013, Noonan et al 2013). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu -PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

^{177}Lu -PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ^{177}Lu -PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ^{177}Lu -PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (^{68}Ga), lutetium-177 (^{177}Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (^{90}Y).

^{177}Lu , the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu is a medium-energy β -emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β -range of ^{177}Lu provides better irradiation of small tumors, in contrast to the longer β -range of ^{90}Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ^{177}Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ^{177}Lu -PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ^{177}Lu to prostate cancer cells.

^{177}Lu -PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ^{177}Lu -PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ^{177}Lu -PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile

and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of ≥ 6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2019](#), [Hofman et al 2018](#), [Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective overall response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ^{177}Lu -PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1–2, of ^{177}Lu -PSMA-617 treatment are dry mouth, nausea,

vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADs and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for

repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Søydal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ^{177}Lu -PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ^{177}Lu -PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG (sub-study of approximately 30 patients).

2.2 Trial endpoints

2.2.1 Alternate Primary endpoint

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression

- Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
 - c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
5. Biochemical response endpoints:
- a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK, and ECG in a sub-study of approximately 30 patients

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone (Figure 1).

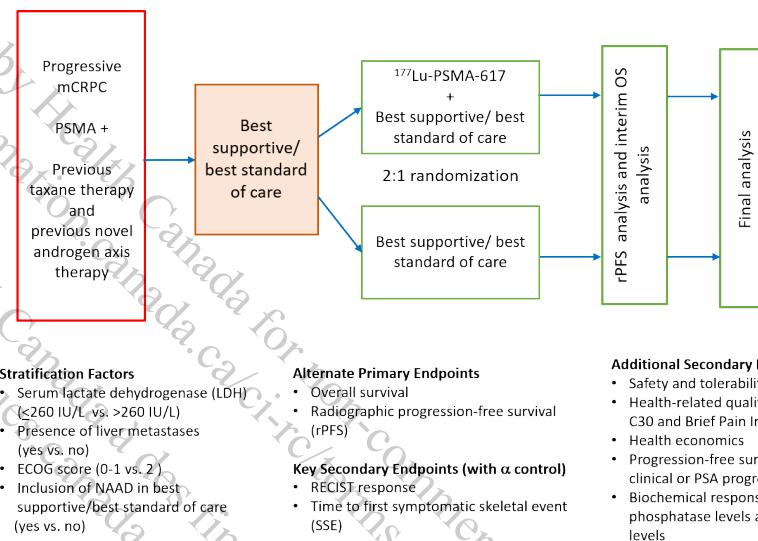


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.1.2 Study design update – Dosimetry, PK and ECG sub-study

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

In order to not bias the results obtained from randomized patients in the main study, the data of the substudysub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The substudysub-study details and analyses will be presented in a separate report. Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific tests conducted in the sub-study, as described in Appendix 12, and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms, with exception to the additional 30 patients in the sub-study who will receive the investigational treatment. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ¹⁷⁷Lu-PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ¹⁷⁷Lu- PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

¹⁷⁷Lu-PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ¹⁷⁷Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018). In addition, a recent review suggests optimal dosing of 6 cycles of ¹⁷⁷Lu-PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ¹⁷⁷Lu-PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ¹⁷⁷Lu-PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ¹⁷⁷Lu-PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Patients included in the sub-study will not undergo randomization as all patients will receive the investigational arm.

Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)

- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

It is anticipated that it will take approximately 14 months to randomize the required 814 patients in the study. After the last patient is randomized, patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga -PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation or intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesion(s) by bone scan (2+2 PCWG3 criteria, Scher et al 2016).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

a. Bone marrow reserve:

- White blood cell (WBC) count $\geq 2.5 \times 10^9/\text{L}$ ($2.5 \times 10^9/\text{L}$ is equivalent to $2.5 \times 10^3/\mu\text{L}$ and $2.5 \times \text{K}/\mu\text{L}$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu\text{L}$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$ ($1.5 \times 10^9/\text{L}$ is equivalent to $1.5 \times 10^3/\mu\text{L}$ and $1.5 \times \text{K}/\mu\text{L}$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu\text{L}$)
- Platelets $\geq 100 \times 10^9/\text{L}$ ($100 \times 10^9/\text{L}$ is equivalent to $100 \times 10^3/\mu\text{L}$ and $100 \times \text{K}/\mu\text{L}$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu\text{L}$)
- Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

b. Hepatic:

- Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

c. Renal:

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$

15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L).

16. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible.

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 3 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:

- a. Are allowed by the protocol.
- b. Have been agreed to by the treating investigator and patient.
- c. Allow for the management of the patient without ^{177}Lu -PSMA-617.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the treatment arm in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to

these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga -PSMA-11

For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure. The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(\pm 5) minutes before and at 30(\pm 5) and 60(\pm 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count $<3.0 \times 10^9/\text{L}$• ANC $<1.5 \times 10^9/\text{L}$	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematologic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Thrombocytopenia (platelet count of < 75 x 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
-------	-------	----------------------------

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, or other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization (enrollment for sub-study patients) except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Adverse Event (AE) monitoring and Serious Adverse Event (SAE) reporting	Begins at time of consent.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ¹⁷⁷ Lu-PSMA-617 within 28 days after randomization.

^a For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.
BPI-SF = Brief Pain Inventory - Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#). The timing of the additional assessments for the sub-study are provided in [Appendix 12](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ⁶⁸Ga-PSMA-11 scan data will be used for additional exploratory analyses. The ⁶⁸Ga-PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ⁶⁸Ga-PSMA-11 PET/CT scans by

assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ⁶⁸Ga-PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ⁶⁸Ga-PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.5 Pain score

Pain will be assessed using the BPI-SF.

The BPI-SF will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort,

anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993, Esper et al 1997](#))
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) analysis will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

- | | | | |
|------------|--|--|---|
| Chemistry | <ul style="list-style-type: none">• sodium• potassium• total and direct bilirubin• ALP• AST• ALT | <ul style="list-style-type: none">• LDH• blood urea nitrogen• creatinine• uric acid• phosphorus• chloride | <ul style="list-style-type: none">• bicarbonate• calcium• glucose• total protein• albumin |
| Urinalysis | <ul style="list-style-type: none">• urine pH• protein content• specific gravity• appearance and color | <ul style="list-style-type: none">• glucose• ketones | |
| Hematology | <ul style="list-style-type: none">• complete blood count (white blood cell count and differential)• red blood cell count• hemoglobin• hematocrit• platelet count | | |

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g., condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 3 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission

to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death;• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ^{68}Ga -PSMA-11 and/or ^{177}Lu -PSMA-617; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of

the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non- confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341

deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p < 0.004$ 1-sided is achieved for rPFS and $p < 0.001$ 1-sided, is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p < 0.004$ 1-sided is achieved for rPFS but $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS but $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS and $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p < 0.020$ to $p < 0.025$ in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS -with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard

deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. PFS eventsThe primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, stratified for the randomization stratification factors.

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to

occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is **not required** to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level **or** OS to meet its allocated alpha level at **either** (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) **or** (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval

and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG in a sub-study of approximately 30 patients presented separately from the main study analyses.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value. DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set. The same analyses will be performed separately in the sub-study of approximately 30 patients.

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ^{68}Ga -PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ^{68}Ga -PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ^{68}Ga -PSMA-11 dosing up to 6 days after the date of ^{68}Ga -PSMA-11 dosing as long as prior to the first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ^{68}Ga -PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ^{68}Ga -PSMA-11 TEAEs. Unrelated ^{68}Ga -PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ^{177}Lu -PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

AEs leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and interim data evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal interim analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

Page 55 of 103

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of

the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are

requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015; 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2019;37(suppl 7S): 228. Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract.* 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research.* 2018 Jul;78(13): CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(6):987–88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of Oncology* 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013;24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXNN Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate

resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Celli D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 65 of 103

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. 177Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [177Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017; DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 66 of 103

Appendix 1 Schedules of Assessments

| Protocol no. PSMA-617-01
Version no.: 4.~~44~~ DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019 22 July 2020

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Cycle Day:						
Concomitant medication review	X-----				X-----	
AE monitoring ^a	X-----				X-----	
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

| Protocol no. PSMA-617-01
Version no. 4.44 DE

Endocyte, Inc.
09-August-2019 22 July 2020
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6			
Cycle Week:							Every 12 weeks (\pm 4 days)		Every 3 months (\pm 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^e					X ^a	X ^a	X	
AE monitoring ^b	X					X ^a	X ^a	X	
Weight	X ^e						X ^e	X	
ECOG	X ^e						X ^e	X	
Directed physical exam	X ^e						X ^e	X	
Vital signs ^d	X ^e						X ^e	X	
EQ-5D-5L	X ^{e,h}						X ^{e,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^e		X ^e		X ^e		X ^e	X	
Chemistry ^f	X ^e		X ^e		X ^e		X ^e	X	
Serum testosterone	X ^e						X ^e	X	
PSA	X ^e						X ^e	X	

Protocol no. PSMA-617-01
Version no.: 4.44 DE

Endocyte, Inc.
09-August-2019 22 July 2020
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

* After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ^{177}Lu -PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone.

** Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.^a Phone evaluation is allowed but are not required for visits after Day 1 of each cycle.

^b Adverse event monitoring will commence at time of consent.

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ^{177}Lu -PSMA-617 administration.

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (± 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell.

Protocol no. PSMA-617-01
Version no.: 4.44 DE

Endocyte, Inc.
09-August-2019 22 July 2020

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 5. Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) – (Not applicable for V4.14 DE)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X-----					X
AE monitoring ^b	X-----					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: Up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will begin at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01
Version no.: 4.14 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019 22 July 2020

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) – (Not applicable for V4.44 DE)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
	Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5			
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Every 3 months (± 1 month)
Concomitant medication review	X-----X ^a						X		
AE monitoring ^b	X-----X ^a						X		
Weight	X ^c						X ^b	X	
ECOG	X ^c						X ^b	X	
Directed physical exam	X ^c						X ^b	X	
Vital signs ^c	X ^c						X ^b	X	
EQ-5D-5L	X ^{e,h}						X ^{d,g}	X ^{d,g}	
FACT-P	X ^{e,h}						X ^{d,g}	X ^{d,g}	
BPI-SF	X ^{e,h}						X ^{d,g}	X	
Best supportive/best standard of care	As per physician's orders								
Hematology ^e	X ^c		X ^b		X ^b		X ^b	X	
Chemistry ^e	X ^c		X ^b		X ^b		X ^b	X	
Serum testosterone	X ^c						X ^b	X	
PSA	X ^c						X ^b	X	

Protocol no. PSMA-617-01
Version no. 4.44 DE

Endocyte, Inc.
09-August-2019 22 July 2020
This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)	
---	--	--

^{**}Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

^a Phone evaluation are allowed but are not required for visits after Day 1 of each cycle. .

^b Adverse event monitoring will commence at time of consent.

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5-Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Page 75 of 103

Appendix 3 Principal investigator signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>
<http://www.fda.gov/Downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 78 of 103

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

|
Protocol no. PSMA-617-01
Version no.: 4.~~44~~ DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Page 79 of 103

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

| Protocol no. PSMA-617-01
Version no.: 4.~~44~~ DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Record outcome as new lesions, no new lesions or resolved lesion• First scheduled reassessment:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ New lesions: perform a confirmatory scan 6 or more weeks later• Confirmatory scan:<ul style="list-style-type: none">◦ No new lesions: continue therapy◦ Additional new lesions: progression• Subsequent scheduled reassessments:<ul style="list-style-type: none">◦ No new lesions: continue◦ New lesions: progression• Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none">• Exclude pseudoprogression in the absence of symptoms or other signs of progression• At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)• If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented• For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan• Date of progression is the date of the scan that first documents the second lesion• Changes in intensity of uptake alone do not constitute either progression or regression• Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none">• Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to Scher et al 2016 for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 82 of 103

Appendix 8 BPI-SF (*sample only, not for patient use*)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use
clinical-information.canada.ca/ci-rc/terms
Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/conditions

| Protocol no. PSMA-617-01
Version no.: 4.~~44~~ DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Brief Pain Inventory (Short Form)

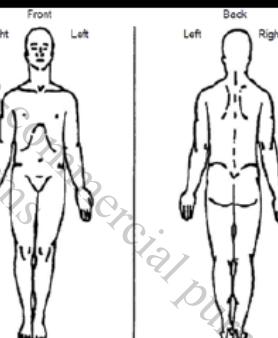
Time: ____ : ____ AM PM

Today's Date (day, month, year):
____ - ____ - ____
JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Today's Date (Day, Month, Year): <u> </u> - <u> </u> - <u> </u> (Example: 08-FEB-2016) <u> </u> DAY <u> </u> MONTH <u> </u> YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 4.44 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Page 85 of 103

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (sample only, not for patient use)

Disclosed by Health Canada for non-commercial purposes and subject to the Terms of Use

clinical-information.canada.ca/ci-rc/terms

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation

renseignements-cliniques.canada.ca/ci-rc/conditions

Protocol no. PSMA-617-01
Version no.: 4.44 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Page 86 of 103



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.44 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Page 87 of 103

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

-
-
-
-
-

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

-
-
-
-
-

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

-
-
-
-
-

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

-
-
-
-
-

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

-
-
-
-
-

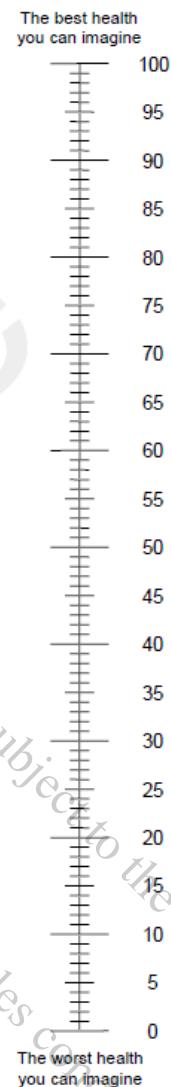
2

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Page 88 of 103

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.44 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09-August-2019

Page 89 of 103

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy -
Prostate) (sample only, not for patient use)**

Protocol no. PSMA-617-01
Version no.: 4.14 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

GE1
GE2
GE3
GE4
GE5
GE6

		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

GF1
GF2
GF3
GF4
GF5
GF6
GF7

		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

19 November 2001
Page 2 of 3

Protocol no. PSMA-617-01
Version no.: 4.14 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
09 August 2019

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNs	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 93 of 103

Appendix 11 PCCTC Bone Scan Assessment Tool

Protocol no. PSMA-617-01
Version no.: 4.14 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

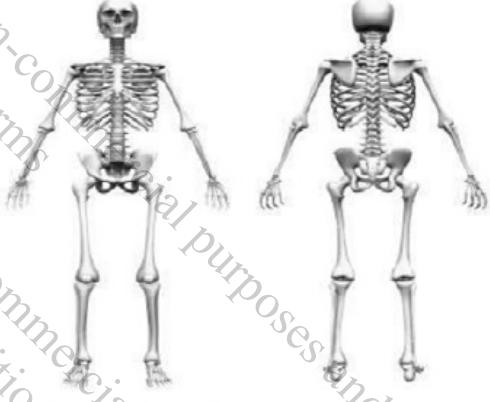
Endocyte, Inc.
09 August 2019

Page 94 of 103

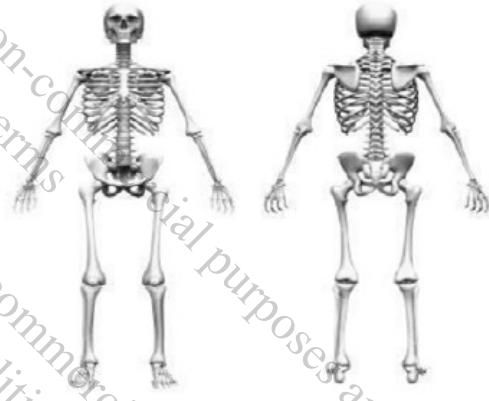
Screening Scan

Bone Scan Date:	D D M M M Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 8 BASELINE Scan

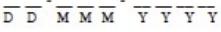
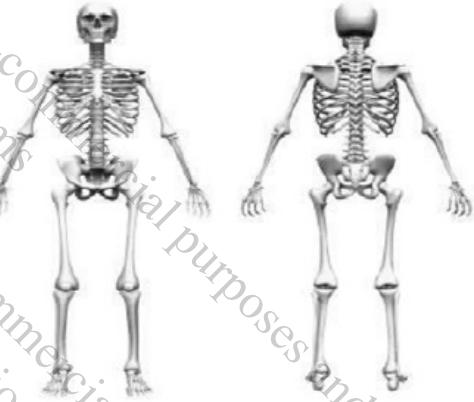
Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening:	Draw site(s) of NEW lesion(s) on skeleton:
<input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
* Presence of new lesions at this time does not confirm progression	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> :	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> AND were there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 97 of 103

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 98 of 103

Week 24 36 48 60 72 84 ____ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE <u>Week 8 Bone Scan</u> : <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton:
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+2) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

APPENDIX 12 DOSIMETRY, PK AND ECG SUB- STUDY

1. DOSIMETRY, PK AND ECG SUB-STUDY DESIGN

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study.

Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific assessments conducted in the sub-study, as described below and the separate sub-study manual, the treatment regimen and patient care management will be identical to that implemented in the main study.

The results of this sub-study will be included in a Dosimetry Study Report addendum that will accompany the main study report.

2. AMENDMENT 4.4 RATIONALE

Due to local radioprotection laws and established guidelines in Germany, institutions are required to conduct additional imaging assessments following each given therapeutic dose of ¹⁷⁷Lu-PSMA-617 in order to investigate proper drug administration for patients participating in clinical trials. In an effort to align and comply with these local guidelines, additional assessments have been added to this sub-study protocol. These include imaging assessments and further surveillance for evaluating renal function.

3. OBJECTIVES

To evaluate dosimetry, pharmacokinetics, urine and ECG.

3.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ¹⁷⁷Lu-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney and bone marrow)

3.2 Secondary Objectives:

- Define the pharmacokinetic profile of ¹⁷⁷Lu-PSMA-617;
- Evaluate ECGs during treatment with ¹⁷⁷Lu-PSMA-617;

- Evaluate the safety and tolerability of ^{177}Lu -PSMA-617;
- Evaluate the metabolic stability of ^{177}Lu -PSMA-617

4. DOSIMETRY, PK AND ECG SUB-STUDY ASSESSMENTS

The sub-study patients will require full whole body (planar) and , 3D SPECT/ and CT imaging, urine collection, blood PK sampling and ECGs, at several time points during cycle 1 of treatment. Urine for complete dosimetry assessment, blood exposure, renal function, urinary metabolites and cardia assessments. Whole body planar and 3D SPECT localized to the abdomen will be collected for HPLC (High performance liquid chromatography)- analysis performed from cycle 2 through cycle 6 of ^{177}Lu -PMSA-617 treatment.

Refer to Table 7 and the sub-study manual for timing assessments.

4.1 Imaging Assessments

Baseline images will be used to determine volumes in regions of interest in selected major source organs such as the liver, spleen and kidneys. Refer to the sub-study manual for further details on measurements and calculations.

~~Serial gamma camera images (whole body planar images) will be obtained in the first treatment cycle detailed in table 7 below. 3D SPECT/CT scans will be also performed in the upper abdomen (comprising kidneys, liver and spleen).~~

~~Full body planar images will be acquired at the following time points after administration:~~

~~1-2 hours~~
~~18-26 hours~~
~~36-48 hours~~
~~156-168 hours~~

~~3D SPECT images will be acquired at the following time points after administration:~~

~~1-2 hours (Additional CT imaging required)~~
~~18-26 hours~~
~~36-48 hours~~
~~156-168 hours~~

4.1.1 Equipment

The following equipment will be required:

1. A gamma-camera with medium energy collimator.

2. A Co-57 flood source or a Lu-177 or Tc-99m filled flood source for the transmission scan.
Well counter with multichannel analyzer or gamma counter to determine ¹⁷⁷Lu radioactivity in blood and urine samples.
3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.

4.2 PK Blood Sampling

Blood PK samples will be collected during cycle 1 of the treatment, to provide data for bone marrow radiation dose calculations and for PK assessment.

At cycle 1, blood samples (1mL) will be collected in heparinized tubes starting immediately before the start of administration, end of administration, then approximately 20mins (+/- 5mins), 60mins(+/- 5mins), 2hr (+/- 30mins), 4hr (+/- 30mins), 24hr (+/- 2hrs), 48hr (+/- 2hrs), 72hr (+/- 2hrs) & day 6 post end of infusion. Blood PK samples should be collected after ECGs, where timepoints overlap. Refer to Table 7 for the timing of assessments.

Radioactivity in blood will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time points have to be recorded by site. The exact time point of each measurement and the calibration factor must be documented by the investigational site.

4.3 Cardiac Assessments

A twelve-lead ECG test will be performed in triplicate for all patients during Cycle 1 of treatment for up to 4 time points (pre-administration and thereafter at approximately 1hr, 4hrs and 24hrs post treatment). Blood Pressure (BP) should be measured prior to each ECG time point.

Patients should have a light breakfast on the morning of treatment.

In the event of a clinically significant finding (i.e., QTcF increase from baseline of >30ms occurs), an additional single safety ECG should be repeated prior to dosing at cycle 2.

All pre-medications will be administered during the time interval ranging from 90 mins to 60 mins before the start of infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen.

If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1hr before the start of infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1hr before, until 8hr after the start of infusion, unless clinically required.

Data obtained will be analyzed by a central reader to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Clinically significant abnormalities will be recorded on the Adverse Event page of the eCRF.

ECG parameters will include HR, RR interval, PR interval, QRS interval and QT interval. QT intervals will be corrected for HR.

4.4 Urine

Total urine excreted will be collected between the end of infusion and the time of the first image (2hrs post infusion).

The extent of elimination of the radiolabeled compound must be determined before acquiring the first image. Therefore, the urine eliminated between the infusion and the time of the first image must be collected quantitatively (possibly in one single container), the whole volume or mass of this excreted urine must be measured and 1 mL sample withdrawn for radioactivity measurement. Radioactivity in urine will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time point of urine collection and measurement, as well as the calibration factor must be documented by the investigational site.

An aliquot (10 mL) of the whole urine collected between the infusion and the time of the first image will be also sent to a central laboratory for HPLC analysis. Moreover, for HPLC analysis purpose only, additional urine samples (around 10 mL, no need to have cumulative urine samples for this assessment) will be collected from the patients at 24hrs (+/-2hrs), 48hrs (+/-2hrs) and 72hrs (+/-2hrs). Collected samples will be sent to a central laboratory for analysis by HPLC according to a validated procedure, in order to determine the elimination of the radioactive compound and possible metabolites, if any, over time.

4.5

4.5 Renal Function Surveillance

In order to assess potential renal toxicity during the treatment phase of the study, the estimated glomerular filtration rate (eGFR) will be calculated from cycle 1 through cycle 6 with the most recent serum creatinine results collected using the Modification of Diet in Renal Disease (MDRD) equation. eGFR should be calculated prior to ¹⁷⁷Lu-PMSA-617 dosing in order to assess renal function.

Table 7:7 Sub-Study Assessment timepoints (time points Cycle 1 only)

Timepoint	Cycle 1 only						Cycle 2 through Cycle 6		
	eGFR calculation	planar fullWhole body planar imaging	3D SPECT/CT imaging	Blood sampling	BP & Intense ECG ^{b,d}	Urine	eGFR calculation	Whole body planar imaging	3D SPECT/CT imaging
Pre dose	X			X	X		X		
End of dose				X					

20 mins (+/- 5 mins)				X		X (end of dose to 2hrs) cumulative collection ^a			
60 mins (+/- 5 mins)				X	X				
2 hours		X (1-2 hours) ^c	X (1-2 hours)+ CT	X (+/-30 mins)					
4 hours (+/- 30 mins)				X	X				
24 hours		X ^c (18-26 hours)	X (18-26 hours)	X (+/-2 hr)	X (+/-2 hr)	X (+/-2 hr)			
48 hours		X (36-48 hours)	X (36-48 hours)	X (+/-2 hr)		X (+/-2 hr)	X (36-48 hr)		X (36-48 hr)
72 hours				X (+/-2 hr)		X (+/-2 hr)			
Day 6				X	X				
156-168 hours	X	X	X						

^a Whole urine collection required between end of infusion and 2hrs post infusion, before the first image

^b Intense ECG monitoring required on day 1 cycle 1 only. Predose (Typically the patient lies supine at least 30 minutes prior to dosing. The triplicate ECGs are collected at approximately 1.5-2 min intervals during the last 5 minutes of the 30 minutes. The next triplicate is collected 1hr post dose, typically the patient is supine for 15 minutes (45 minutes post dose) and 3 readings are taken in last 5 minutes. The next triplicate is at 4hrs and the final at 24hrs and patient is supine resting for 15 minutes - after 10 minutes take 3 readings. ECG monitoring should be performed prior to blood collection.

^c After urine collection

BP to be collect prior to each ECG

4.6 Measurements, Recording, Calculation and Analysis of Sub-study Data

Details regarding the methods used to measure, record and perform necessary calculations of the data acquired can be found in the sub-study manual.



PROTOCOL NO. PSMA-617-01:

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL, MULTICENTER, RANDOMIZED PHASE 3 STUDY OF ¹⁷⁷Lu-PSMA-617 IN THE TREATMENT OF PATIENTS WITH PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)

Clinical Protocol No.: PSMA-617-01

Version No.: 4.4 DE

Date: 22 July 2020

IND No.: 133,661 (¹⁷⁷Lu-PSMA-617)

EudraCT No.: 2018-000459-41

Phase of Study: Phase 3

Investigational Products: ¹⁷⁷Lu-PSMA-617

Sponsor: Endocyte, Inc.
3000 Kent Avenue - Suite A1-100
West Lafayette, Indiana 47906-1075
(765) 463-7175

Medical Officer: Richard Messmann, MD, MHS, MSc
Vice President, Medical Affairs
Endocyte, Inc., A Novartis Company
8910 Purdue Road, Suite 250
Indianapolis, Indiana 46268
[Contact]
[Contact]

Approval:

[signed electronically in MasterControl]

Medical Officer Signature

Date

Confidentiality Statement

By accepting receipt of this document, you (recipient) agree not to disclose the contents (in whole or in part), directly or indirectly, by any means except as authorized in writing by the owner, Endocyte, Inc. This document contains commercial and proprietary, or privileged, information and trade secrets that may not be disclosed by recipient unless such disclosure is required by federal or state law, and then only to the extent required by law, or allowed by Endocyte. Recipient will restrict access to this protected information only to those employees of recipient who are required to consider this information for purposes of your interactions with Endocyte. Recipient will take all steps necessary to ensure that these employees protect the information contained herein and do not disclose it to others. Recipient will ensure that each of its employees to whom this information is disclosed is told of its protected status and that all such employees agree not to disclose the information to any unauthorized person or entity. These disclosure restrictions apply equally to all related future information supplied to you, which Endocyte indicates as privileged or confidential.

Page 2 of 104

Site Principal Investigator Signature

The investigator signature page is provided in [Appendix 3](#) along with a link to form FDA 1572 or equivalent if the site is outside of the United States.

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 July 2020

Table of Contents

Site Principal Investigator Signature	2
Table of Contents.....	3
Revision History	8
Clinical Trial Summary.....	10
List of Abbreviations and Definitions	13
1. Introduction	15
1.1 Background information	15
1.2 Summary of nonclinical studies with clinical significance.....	19
1.3 Summary of known and potential risks and benefits	20
2. Trial Objectives and Endpoints	21
2.1 Trial objectives.....	21
2.1.1 Primary objective	21
2.1.2 Key secondary objectives.....	21
2.1.3 Additional secondary objectives	21
2.2 Trial endpoints	21
2.2.1 Alternate Primary endpoint	21
2.2.2 Key Secondary endpoints	22
2.2.3 Additional Secondary endpoints	22
3. Trial Design.....	23
3.1 Overview of the clinical trial design.....	23
3.1.1 Study design update.....	26
3.1.2 Study design update - Dosimetry, PK and ECG sub-study	26
3.2 Rationale for the study design.....	27
3.3 Measures taken to minimize/avoid bias	27
3.4 Description of the clinical trial	27
3.4.1 Description of investigational medicinal product.....	27
3.4.2 Dosage and rationale for dose selection	27
3.4.3 Subject allocation to treatment	28
3.4.4 End of treatment visit	29
3.4.5 Duration of Subject Participation	29
3.5 End of trial definition.....	29
4. Selection and discontinuation of Subjects.....	29
4.1 Inclusion criteria	30
4.2 Exclusion criteria	31

4.3	Subject withdrawal of consent for study or treatment	32
5.	Treatment of Subjects	33
5.1	Treatment with the investigational medicinal product.....	33
5.1.1	Administration of ⁶⁸ Ga-PSMA-11.....	33
5.1.2	Administration of ¹⁷⁷ Lu-PSMA-617	33
5.1.3	Toxicity risk reduction and supportive care for ¹⁷⁷ Lu-PSMA-617 injections ...	33
5.1.4	Management of toxicity adverse events: dosing delays and modification	34
5.2	Best supportive/best standard of care.....	36
5.3	Concomitant medications/ supportive care	37
5.3.1	Permitted concomitant medications/ supportive care.....	37
5.3.2	Prohibited concomitant medications	37
5.4	Monitoring treatment compliance	37
5.5	Treatment discontinuation	37
6.	Study Assessments and Procedures	38
6.1	Screening procedures and baseline assessments	38
6.2	Efficacy assessments.....	40
6.2.1	Radiographic imaging for tumor assessments	40
6.2.2	Additional Imaging Analyses	40
6.2.3	RECIST criteria	41
6.2.4	Symptomatic skeletal events	41
6.2.5	Pain score	41
6.2.6	Health-related quality of life	41
6.2.7	Health Economics.....	42
6.2.8	Clinical progression	43
6.2.9	PSA levels	43
6.3	Safety assessments	43
6.3.1	Clinical laboratory evaluations	43
6.3.2	Vital signs	44
6.3.3	Electrocardiograms	44
6.3.4	Birth Control	44
6.4	End of treatment visit procedures	44
6.5	Long-term follow-up procedures	44
7.	Adverse Events	45
7.1	Adverse event definitions	45
7.2	Evaluating and recording adverse events	46
7.3	Immediate Adverse Event Reporting	46

7.3.1	Serious Adverse Events.....	46
7.3.2	Serious adverse event subject follow-up	47
7.3.3	Sponsor Contact Information for Immediate Reporting.....	47
8.	Statistics	47
8.1	Revision to the protocol and statistical analyses of rPFS and OS.....	47
8.2	Revisions to planned analyses	48
8.3	Sample size and power determination	48
8.4	Analysis populations.....	49
8.5	Demographics and baseline disease characteristics	49
8.6	Patient disposition.....	50
8.7	Efficacy analyses	50
8.7.1	Alternate primary endpoint analysis.....	50
8.7.2	Secondary efficacy analyses.....	51
8.8	Safety analyses.....	53
8.8.1	Extent of exposure.....	53
8.8.2	Analysis of adverse events	53
8.8.3	Analysis of laboratory assessments.....	53
8.8.4	Analysis of vital sign data	54
8.9	IDMC and interim data evaluation	54
8.9.1	IDMC	54
8.9.2	Formal interim analysis of OS	54
9.	Access to Source Data/Documents	54
10.	Ethics.....	55
10.1	Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)	55
10.2	Informed consent	55
10.3	Health Insurance Portability and Accountability Act.....	55
10.4	Confidentiality.....	56
11.	Compliance and quality control	56
11.1	Compliance with Monitoring and Audits	56
12.	Data Handling, Record Keeping, and Compliance	57
12.1	Investigational medicinal product accountability.....	57
12.2	Breaking the blind	57
12.3	Data collection forms and source document identification	57
12.4	Record maintenance and retention	58
12.5	Archiving	58

13. Publication Policy.....	58
14. References	59
Appendix 1 Schedules of Assessments	66
Appendix 2 Suggested treatment guidelines	75
Appendix 3 Principal investigator signature	76
Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	77
Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison	78
Appendix 5 Common Terminology Criteria for Adverse Events	79
Appendix 6 Response Evaluation Criteria in Solid Tumors	80
Appendix 7 Prostate Cancer Working Group 3 Recommendations.....	81
Appendix 8 BPI-SF (<i>sample only, not for patient use</i>).....	83
Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) - 5 Domain 5 Level scale) (<i>sample only, not for patient use</i>)	86
Appendix 10 FACT-P (Functional Assessment of Cancer Therapy - Prostate) (<i>sample only, not for patient use</i>)	90
Appendix 11 PCCTC Bone Scan Assessment Tool.....	94
Appendix 12 Dosimetry, PK and ECG Sub- study	100
1. DOSIMETRY, PK and ECG SUB-STUDY DESIGN.....	100
2. Amendment 4.4 RATIONALE	100
3. Objectives.....	100
3.1 Primary Objective:	100
3.2 Secondary Objectives:	100
4. DOSIMETRY, PK and ECG SUB-STUDY ASSESSMENTS	101
4.1 Imaging Assessments.....	101
4.1.1 Equipment	101
4.2 PK Blood Sampling	101
4.3 Cardiac Assessments.....	102
4.4 Urine	102
4.5 Renal Function Surveillance	103
4.6 Measurements, Recording, Calculation and Analysis of Sub-study Data	104

List of tables

Table 1 Toxicity management and dose modification recommendations	34
--	----

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 July 2020

Table 2	Screening procedures and baseline assessments	38
Table 3	Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycle 1)	67
Table 4	Schedule of assessments: ¹⁷⁷ Lu-PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU).....	69
Table 5	Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) - (Not applicable for V4.4 DE).....	72
Table 6	Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) - (Not applicable for V4.4 DE).....	73
Table 7	Sub-Study Assessment time points	103

List of figures

Figure 1	Diagram of trial design.....	24
----------	------------------------------	----

Revision History

Version No.	Date	Summary of Changes
1.0	22 March 2018	Not applicable; initial clinical trial protocol.
1.1	03 July 2018	GB only amendment AE assessment timing to start from consent. Added wording regarding birth control
1.2	26 September 2018	DE only amendment AE assessment timing to start from consent. Added wording regarding birth control
2.0	16 January 2019	Incorporated GB and DE only amendment changes. Added statement of compliance as required by Sweden. Incorporated the addition of the alternative primary endpoint of rPFS and update to 1 rPFS analysis and 1 overall survival analysis. Clarified inclusion of and timing of start for best supportive/best standard of care. Clarified inclusion/exclusion criteria. Clarified procedures and timing Clarified progression of disease is not considered an AE or SAE. Clarified start and end timing for ⁶⁸ Ga-PSMA-11 TEAEs, ¹⁷⁷ Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.
3.0	01 April 2019	<ul style="list-style-type: none">• Updated sponsor name.• Updated background information data.• Clarified rPFS is an alternate primary endpoint.• Clarified inclusion/exclusion criteria and added specific criteria regarding best supportive/best standard of care options to be identified for patients as part of eligibility.• After Cycle 6, visits are now every 12 weeks (+/- 4 days)• Additional details regarding long-term follow were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This now includes radiographic follow up.• Plasma testosterone was added as an acceptable form of testosterone testing.• Window for QOL and Pain questionnaires added. <p>Updated reference section</p>
4.0	08 July 2019	<ul style="list-style-type: none">• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients.• Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after March 5th, 2019 were added.• Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%)

		<p>and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023.</p> <ul style="list-style-type: none">• Additional imaging analyses details were added for study ⁶⁸Ga PSMA 11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria.• Further clarification on the start and end timing for ⁶⁸Ga-PSMA-11 TEAEs, ¹⁷⁷Lu-PSMA-617 TEAEs and best supportive/best standard of care dosing and intervention TEAEs.• Additional wording to clarify intent to collect radiographic imaging for patients who stop treatment for reasons other than radiographic progression.
4.1	09 August 2019	<p>DE amendment – all protocol changes noted above for Versions 2, 3 and 4 are also included in DE amendment 4.1</p> <p>Added a dosimetry, pharmacokinetics (PK) and electrocardiogram (ECG) sub-study which will include a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients from selected sites in Germany. Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.</p>
4. 4 DE	22 July 2020	<p>DE amendment -1 – all modifications for Version 4.4 DE pertain to the Dosimetry sub-study and accordingly are included in Appendix 12 of this document.</p> <ul style="list-style-type: none">• Additional imaging procedures of whole body planar and 3D SPECT from cycle 2 through cycle 6 of PSMA-617 treatment to align and comply with local radioprotection laws and established guidelines in Germany.• Implementation of estimated glomerular filtration rate (eGFR) from cycle 1 through cycle 6 of PSMA-617 treatment to further assess potential renal toxicity.

Clinical Trial Summary

Protocol title:	VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ¹⁷⁷ Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)
Clinical phase:	Phase 3
Objectives:	<p>The primary objective of this study is to compare overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/best standard of care versus patients treated with best supportive/best standard of care alone.</p> <p>Key secondary objectives are an arm-to-arm comparison of the following:</p> <ul style="list-style-type: none">• Radiographic progression-free survival (rPFS)• Response Evaluation Criteria in Solid Tumors (RECIST) response• Time to a first symptomatic skeletal event (SSE) <p>Additional Secondary Objectives:</p> <ul style="list-style-type: none">• Safety and tolerability of ¹⁷⁷Lu-PSMA-617• Health-related quality of life (HRQoL; EQ-5D-5L, FACT-P and Brief Pain Inventory – Short Form (BPI-SF))• Health economics• Progression-free survival (PFS) (radiographic, clinical, or prostate-specific antigen [PSA] progression-free survival)• Biochemical response as measured by PSA. Alkaline phosphatase [ALP] levels and lactate dehydrogenase [LDH] levels will also be measured.• Dosimetry, PK and ECG in a sub-study of approximately 30 patients
Study design:	<p>Patients with PSMA positive scans will be randomized in a 2:1 ratio to receive either ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care or to receive best supportive/best standard of care only. Best supportive/best standard of care will be determined by the treating physician/investigator but will exclude investigational agents, cytotoxic chemotherapy, other systemic radioisotopes, and hemi-body radiotherapy. Novel androgen axis drugs [NAADs] (such as abiraterone or enzalutamide) are allowed.</p> <p>The study is open-label and patients will be monitored throughout the 6 to 10-month treatment period for survival, disease progression, and adverse events.</p> <p>rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS.</p> <p>When a patient discontinues from the treatment portion of the study, they will have an end of treatment visit and will then continue to be followed in long-term follow-up. A long-term follow-up period will include the collection of rPFS survival and treatment updates, adverse events assessment, as well as blood for hematology and chemistry testing. During follow-up, patients will be contacted every 3 months (± 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs). These patients will be asked to sign a separate consent detailing what kind of long term follow up</p>

	<p>assessments and study updates they will agree to. They will also be able to designate a contact person (e.g. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.</p> <p>An End of Treatment visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).</p> <p>This visit should occur approximately 30 days from the last dose of ^{177}Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.</p> <p>The planned enrollment for this study is 814 patients.</p> <p>A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (^{177}Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617.</p> <p>In order to not bias the results obtained from randomized patients in the main study, the data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The sub-study details and analyses will be presented in a separate report.</p>
Study population:	The study population includes patients with progressive PSMA-positive mCRPC who received at least one novel androgen axis drug [NAAD] (such as enzalutamide or abiraterone) and were previously treated with 1 to 2 taxane regimens. Patients treated with only 1 prior taxane regimen are eligible if the patient is unwilling or the patient's physician deems the patient unsuitable to receive a second regimen.
Investigational product:	Patients randomized to receive the investigational product will receive 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 intravenously every 6 weeks (± 1 week) for a maximum of 6 cycles. After 4 cycles, patients will be assessed for (1) evidence of response, (2) residual disease, and (3) tolerance to ^{177}Lu -PSMA-617. If the patient meets the criteria above and agrees to continue with additional treatment of ^{177}Lu -PSMA-617 radioligand therapy, the investigator may administer 2 additional cycles. A maximum of 6 cycles of radioligand therapy is allowed. After the last cycle of ^{177}Lu -PSMA-617, patients can continue best supportive/best standard of care alone. If the patient does not meet all of the criteria or does not agree to additional ^{177}Lu -PSMA-617 treatment, then no additional doses of ^{177}Lu -PSMA-617 will be administered after Cycle 4. These patients can continue on best supportive/best standard of care alone after Cycle 4.
Assessment schedule:	Radiographic imaging will be done every 8 weeks (± 4 days) during the first 24 weeks of treatment and every 12 weeks (± 4 days) thereafter, regardless of treatment delays, through the End of Treatment visit. The previous 2 PSA values will be noted before randomization. Serum testosterone and PSA levels will be measured within 3 days prior to Day 1 of each cycle. Hematology and chemistry will be done weekly during Cycle 1 (within 3 days prior to each time point) and within 3 days prior to Days 1, 15, and 29 in Cycles 2 to 6

Page 12 of 104

(i.e. every two weeks). After Cycle 6, hematology and chemistry will be done every 8 weeks (± 1 week) until the patient starts long term follow up. Patients will complete the BPI-SF, EQ-5D-5L and FACT-P questionnaires about their pain level and HRQoL during screening and prior to treatment on Day 1 of each cycle and through the End of Treatment visit. Patients will be monitored throughout the study for SSEs. Aside from the specific tests conducted in the sub-study, as described in Appendix 12 and the separate sub-study manual, the treatment regimen and patient care management of patients in the sub-study will remain identical to that implemented in the main study.
Statistical methodology: Subsequent to the implementation of measures to minimize early dropouts from the best supportive/best standard of care alone arm, the primary analysis of rPFS will focus on patients randomized on or after March 5 th , 2019; rPFS will be analyzed in these patients once 364 events have accrued and the alpha level applied will be 0.004 1-sided. At time of the rPFS analysis, there will be an interim analysis of OS and the alpha level applied will be 0.001 1-sided; unlike rPFS, the analysis of OS will include all randomized patients (i.e., including those randomized before March 5 th , 2019). Following the analysis of rPFS and the interim analysis of OS, a final analysis of OS will be performed when 508 death events have accrued and the alpha level applied will be 0.02 1-sided. This trial has 90% overall power and an overall Type I error rate of 0.025 1-sided.
Duration of Study: Total duration of the study will be approximately 38 months.

List of Abbreviations and Definitions

Abbreviation	Term/Definition
ANC	Absolute neutrophil count
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASCO	American Society of Clinical Oncology
BfS	Federal Office for Radiation Protection (Bundesamt für Strahlenschutz)
BPI-SF	Brief Pain Inventory - Short Form
CFR	United States Code of Federal Regulations
CR	Complete response
CRF	Case Report Form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DE	Germany
DOT	Duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EQ-5D-5L	European Quality of Life (EuroQoL) – 5 Domain 5 Level scale
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FACT-P	Functional Assessment of Cancer Therapy – Prostate
GCSF	Granulocyte colony-stimulating factors
FDA	Food and Drug Administration
FAS	Full Analysis Set
⁶⁸ Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPLC	High pressure liquid chromatography
HR	Hazard ratio
hr	hour
HRQoL	Health-related quality of life
IB	Investigator's Brochure

Abbreviation	Term/Definition
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
¹⁷⁷ Lu	Lutetium-177
mCRPC	Metastatic castration-resistant prostate cancer
Min(s)	Minute(s)
NAAD	Novel androgen axis drug (such as abiraterone or enzalutamide)
ORR	Overall response rate
OS	Overall survival
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SPEC	Single-photon emission computed tomography
SSE	Symptomatic Skeletal Event
TEAE	Treatment-emergent adverse event
SOD	Sum of the diameter
ULN	Upper limit of normal
US	United States
WBC	White blood cell
⁹⁰ Y	Yttrium-90

The following clinical protocol describes the scientific rationale, objectives, design, statistical considerations, and organization of the planned trial including the plan to assure the safety and health of the trial participants. Additional details for conducting the clinical trial are provided in documents referenced in the protocol, such as an Investigator's Brochure (IB), the Pharmacy Manual, or in the Appendices.

The format and content of this clinical trial protocol complies with the Guideline for Good Clinical Practice (GCP) [E6(R2)] issued by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) as well as applicable local regulations, i.e. LVFS 2011:19 (Sweden), and the latest version of the Declaration of Helsinki. The study will be conducted according to this clinical trial protocol. The term subject, participant, and patient are used interchangeably throughout this protocol and are used to denote an individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1. INTRODUCTION

1.1 Background information

Prostate cancer and unmet medical need

An estimated 1.1 million men worldwide were diagnosed and 307,000 died due to prostate cancer in 2012. Almost 70% of the cases are diagnosed in more developed regions due to the use of prostate-specific antigen (PSA) testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease ([Ferlay et al 2013](#), [Bray et al 2012](#)).

There is an urgent need for more effective treatments to improve outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the third leading cause of cancer mortality in United States (US) men ([Siegel et al 2017](#)), driven by prostate cancer patients who no longer respond to hormonal therapy. Once patients reach the mCRPC stage, their expected overall survival is low as was seen in the randomized phase 3 study of cabozantinib vs prednisone in men with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median overall survival of the prednisone control arm was 9.8 months ([Smith et al 2016](#)). Post-docetaxel mCRPC patients have an annual death rate of 73% ([Scher et al 2015](#)).

The median age at diagnosis of mCRPC is 70 years ([Flaig et al 2016](#)). Metastatic prostate cancer has a predilection for bone. As a result, approximately 90% of mCRPC patients develop bone metastases ([Kirby et al 2011](#)), and 49% of them will develop a serious skeletal event within 2 years ([Saad et al 2004](#)). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being ([Weinfurt et al 2005](#)). These patients, many of whom are elderly, can be extremely symptomatic and at risk of serious oncological complications. They can be a considerable challenge in the clinic due to the symptoms of metastatic soft tissue and visceral

disease, general frailty, bone marrow impairment, and because they have exhausted approved agents. In mCRPC patients facing advanced illness with little hope for a cure, the focus of treatment shifts from active anti-cancer treatment to palliative care for relief of physical symptoms, maintaining function, and attempting to improve their health-related quality of life (Cella et al 2009). Therefore, in addition to tracking essential clinical outcomes, it is also important to assess and evaluate changes in HRQoL of such fragile patients as they receive treatment.

Several agents have been approved for the treatment of mCRPC, and NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use. Regardless, none of these therapies are proven to prolong survival after enzalutamide or abiraterone. In practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting; Sipuleucel-T is best used in mildly asymptomatic small volume disease; and ²²³Radium is used to treat men with bone-only disease. Taxane-based chemotherapy is most often used today after abiraterone or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly than cabazitaxel. Because both agents have a typical chemotherapy side effect profile, they are often not considered for patients due to comorbidity, poor hematological reserve, or patient refusal (Zielinski et al 2014).

Six small published series with a total of 499 patients have examined the efficacy of either abiraterone or enzalutamide in men previously exposed to a taxane and either abiraterone or enzalutamide. These modern hormonal agents produced only modest activity, including PSA decline >50% in 3% to 22% of patients, a median PFS of 2.7 to 4.6 months and a median OS of 7.2 to 12.2 months (Azad et al 2015, Cheng et al 2015, Badrising et al 2014, Brasso et al 2015, Loriot et al 2013, Noonan et al 2013). It's important to note that this is in contrast with the level of anti-tumor activity demonstrated in the pivotal clinical trials for these agents that led to approval. In that setting, patients had only received prior docetaxel and had not been exposed to prior therapy with either abiraterone or enzalutamide. As these modern hormonal agents have been used in earlier lines of therapy, the use of a second agent following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Therefore, there are limited options available to patients who fail or refuse taxane-based chemotherapy, particularly if alternative agents currently approved in this setting (abiraterone and enzalutamide) have been used earlier in the disease.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in nearly all prostate cancers, but has restricted, and several hundred-fold lower, expression in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009). Additionally, PSMA overexpression also correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for men with mCRPC.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ¹⁷⁷Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003). This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

The result of both selective expression and ligand-based uptake using PSMA as a target is a reduction in background uptake and off-target toxicities as well as an increase in the amount of radioactivity that localizes at the tumor site.

¹⁷⁷Lu-PSMA-617 mechanism of action

The novel PSMA-targeted radioligand therapy ¹⁷⁷Lu-PSMA-617 consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a naphthyl-containing linker. By design, ¹⁷⁷Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). PSMA-617 was uniquely developed for both imaging and radioligand therapy of prostate cancer, and can be radiolabeled with gallium-68 (⁶⁸Ga), lutetium-177 (¹⁷⁷Lu), indium-111, copper-64, scandium-44, actinium-225, or yttrium-90 (⁹⁰Y).

¹⁷⁷Lu, the radioactive cargo being delivered by PSMA-617, has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ¹⁷⁷Lu is a medium-energy β-emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter β-range of ¹⁷⁷Lu provides better irradiation of small tumors, in contrast to the longer β-range of ⁹⁰Y (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than in the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. ¹⁷⁷Lu has a relatively long physical half-life of 6.6 days that combines with the intratumoral retention of ¹⁷⁷Lu-PSMA-617 to reduce the necessary dosing frequency. It is these physical properties, and the benefit of PSMA-targeting, that allow for the delivery of effective activities of ¹⁷⁷Lu to prostate cancer cells.

¹⁷⁷Lu-PSMA-617 for metastatic castration-resistant prostate cancer

The novel therapeutic drug ¹⁷⁷Lu-PSMA-617 was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with metastatic prostate cancer (Kratochwil et al 2015, Hillier et al 2009). Based on preclinical data that demonstrated high PSMA binding affinity and compound internalization, prolonged tumor uptake, rapid kidney clearance, and high tumor-to-background ratio, ¹⁷⁷Lu-PSMA-617 proceeded into clinical development at investigative sites in Germany.

Data evaluations based on compassionate use according to the German Medicinal Product Act, AMG §13 2b, Clinical Trial Notification (Australia) regulations, and other countries where expanded access programs are in place per local regulations, reported a favorable safety profile

and promising results for PSA response rates of systemic radioligand therapy with ^{177}Lu -PSMA-617 in patients with mCRPC.

Dosimetry data suggest that ^{177}Lu -PSMA-617 is targeted to PSMA-expressing tissue, which may include the salivary glands, kidneys, and small and large bowel. The highest exposure is to salivary glands, however in compassionate use studies xerostomia appears low grade and occurs at a rate of approximately 8% in treated patients. Clearance of ^{177}Lu PSMA-617 from the kidney occurs rapidly. To date nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. The exposure to normal bone marrow tissue is predictably low as it does not express PSMA, and corresponds with normal plasma clearance. There was some evidence of reversible hematological toxicity that occurred following ^{177}Lu -PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively.

The first published clinical series of ^{177}Lu -PSMA-617 consisted of 10 patients ([Ahmadzadehfar et al 2015](#)) treated between November 2013 and January 2014, with 5.6 GBq/150mCi (4.1–6.1 GBq/110–165 mCi). PSA decline >50% occurred in 50% of subjects, which increased to 60% after 2 cycles of 6 GBq/160 mCi (4.1–7.1 GBq/110–190 mCi). The level of PSA decline >50% (most commonly used to assess tumor response in these studies) has remained remarkably consistent across several clinical series when 2 or more doses of \geq 6 GBq/160 mCi are given.

Hofman presented the first prospective open-label, single-arm, non-randomized Phase 2 study of ^{177}Lu -PSMA-617 in 30 metastatic castration-resistant prostate cancer patients dosed with up to 4 cycles of 4–8 GBq/110–220 mCi administered every 6 weeks ([Hofman et al 2018](#), [Hofman et al 2019](#)). The primary endpoints of this study were to evaluate both safety and efficacy, as measured by PSA response, bone pain score, quality of life measurements, imaging response and survival.

Of the screened patients, 70% were identified as PSMA-positive via PET imaging and eligible for treatment. Most subjects had been exposed to at least 1 taxane chemotherapy and either abiraterone or enzalutamide in the mCRPC setting. In this heavily pre-treated patient population with few therapeutic alternatives, 64% of patients on ^{177}Lu -PSMA-617 showed a PSA response defined by a reduction in PSA of at least 50%, and 44% had a reduction of PSA of 80% or more. In 27 patients with measurable disease, the objective overall response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was 56% (complete response [CR] and partial response [PR]). Median overall survival was 13.3 months (95% confidence interval [CI] 10.5–18.0). Therapy with ^{177}Lu -PSMA-617 was well tolerated. These safety and efficacy data also translated into significantly improved quality of life scores and reduction in pain scores.

In summary, over 40 compassionate use publications and prospective Phase 2 clinical trial data describe the use of ^{177}Lu -PSMA-617 in patients who have been exposed to approved agents. In the post-taxane, post-androgen axis inhibitor setting ^{177}Lu -PSMA-617 has demonstrated a well-established, predictable, well tolerated safety profile. Clinical series indicate the most common side effects, predominately Grade 1–2, of ^{177}Lu -PSMA-617 treatment are dry mouth, nausea,

vomiting, diarrhea, constipation, fatigue, anemia, thrombocytopenia and neutropenia. The incidence of Grade 3/4 toxicity in the series were very low, and mainly restricted to reversible hematological events. Efficacy has been demonstrated on multiple clinically significant endpoints, including PSA response, soft tissue lesion response measured by RECIST, PFS, OS, pain and quality of life. No standard dose and schedule have been developed.

The preliminary clinical evidence indicates ¹⁷⁷Lu-PSMA-617 may demonstrate clinical benefit in patients with mCRPC in a setting where patients had been exposed to chemotherapy and NAADS and there is no recommended standard of care.

This Phase 3 study will assess the efficacy of ¹⁷⁷Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC by measuring overall survival and rPFS in a randomized, prospective, open-label trial.

1.2 Summary of nonclinical studies with clinical significance

In vitro PSMA affinity and internalization studies

According to Benešová et al, the results of the binding assay of PSMA-617 in PSMA-positive LNCaP cells demonstrated a very high binding affinity, with an equilibrium dissociation constant (K_i) value of 2.34 ± 2.94 nM. The internalization of PSMA-617 is highly effective with an internalized fraction of 17.51 ± 3.99 percent of the added activity/ 10^6 LNCaP cells ($n = 3$) at 37°C (Benešová et al 2015).

Organ distribution in mice bearing PSMA-positive LNCaP tumors

The organ distribution with ¹⁷⁷Lu-PSMA-617 in mice showed a high specific uptake in LNCaP tumors and in the murine kidneys, as expected. Importantly, the high initial kidney uptake is almost completely cleared within 24 hours whereas the tumor uptake remained high or even tended to slightly increase during that time frame. Other organs such as the liver, lung and spleen demonstrated low uptake at 24 hours after injection (Benešová et al 2015).

Biodistribution in Wistar rats

Pharmacokinetic evaluation of ¹⁷⁷Lu-PSMA-617 in normal healthy male Wistar rats exhibited major renal clearance with no significant uptake in any of the major organ/tissue (Das et al 2016). More than 80% of the injected activity was excreted within 3 hours post-injection. Retention of residual activity was observed in intestine, liver, kidneys and skeleton at 24 hours post-administration. However, uptake in these organs, except skeleton, was observed to gradually decrease with the time.

Repeat-dose toxicity in Wistar rats

The toxicity of non-radioactive PSMA-617 administered once weekly by intravenous (IV) administration to male Wistar rats over 22 days was tested in a toxicology study. The animals were treated with 40, 160, or 400 µg PSMA-617/kg b.w. by IV bolus injection on test days 1, 8, 15, and 22. The control group was treated with physiological saline. The no-observed-adverse-effect-level was found to be above 400 µg PSMA-617/kg body weight administered once weekly by IV bolus injection (Leuschner 2016). The estimated mass of the PSMA-617 precursor which is applied per treatment cycle is likely to be approximately 150 to 250 µg. Using the NOAEL for

repeat dosing of PSMA-617 of 400 µg/kg in rats, this accounts for a safety margin of approximately 16-27 fold, assuming that the average patient has a body surface area of 1.7 m². However, considering that a more intensive dosing schedule was tested in rats, relative to the proposed, and well-studied, clinical regimen of once every 6 to 8 weeks, this safety margin may be a conservative estimate.

1.3 Summary of known and potential risks and benefits

Preclinical work, dosimetry studies, and clinical experience with ¹⁷⁷Lu-PSMA-617 since 2013, suggest positive response rates and a favorable safety profile in patients with mCRPC (Kratochwil et al 2016, Rahbar et al 2017, Kulkarni et al 2016, Haug et al 2016, Rathke et al 2017, Soyalal et al 2016, Rathore et al 2016, Rahbar et al 2016a, Ahmadzadehfar et al 2016, Ferdinandus et al 2017, Rahbar et al 2016b, Yadav et al 2017).

Dosimetry studies have confirmed that ¹⁷⁷Lu PSMA-617 is targeted and normal tissues that express PSMA are exposed to radiation (Delker et al 2016). These tissues are salivary glands, renal, and small and large bowel. Renal absorbed dose is cleared rapidly and exposure appears similar to that seen with ¹⁷⁷Lu-DOTATATE. The exposure to normal bone marrow tissue should be low and correspond with normal plasma clearance.

Nephrotoxicity has not been notable in any safety series. There are no reports of Grade 3/4 nephrotoxicity in the literature. There was some evidence of reversible hematological toxicity that occurred following ¹⁷⁷Lu-PSMA-617 treatment that manifested as leukopenia and thrombocytopenia, with rates of 0 to 40% and 4% to 70% respectively. Rahbar (2017) reported ¹⁷⁷Lu-PSMA-617 was associated with asymptomatic Grade 3 or 4 leukopenia, anemia, thrombocytopenia in 3%, 10%, 4%, respectively. Mild reversible xerostomia occurred in 8% of subjects. No significant diarrhea or renal impairment were reported from a retrospective review of doctor reports (Rahbar et al 2017).

Dr. Hofman recently presented results from the first prospective clinical trial with ¹⁷⁷Lu-PSMA-617 (Hofman et al 2019). In the trial, 50 mCRPC patients were dosed with up to 4 cycles of 4–8 GBq. Prospective common toxicity criteria for adverse events (CTCAE) v4 safety data was defined. He found his regimen to be well-tolerated. The most common non-hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included transient G1-2 dry mouth (66%), G1-2 nausea (48%), G1-3 fatigue (38%), and G1-2 vomiting (26%). The most common hematological toxicities attributed to ¹⁷⁷Lu-PSMA-617 occurring in >25% of patients included G1-3 lymphocytopenia (72%), G1-4 thrombocytopenia (38%), G1-3 neutropenia (30%) and G1-3 anemia (28%). G3-4 toxicities attributed to ¹⁷⁷Lu-PSMA-617 were infrequent with lymphocytopenia (32%), thrombocytopenia (10%), anaemia (10%), neutropenia (6%) and fatigue (2%).

Potential risks of ¹⁷⁷Lu-PSMA-617 include the effects of radiological toxicity, namely xerostomia, fatigue, myelosuppression and mild nausea and vomiting.

Additional details of the nonclinical and clinical experience with ¹⁷⁷Lu-PSMA-617 are provided in the IB.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 Trial objectives

2.1.1 Primary objective

The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone.

2.1.2 Key secondary objectives

Key secondary objectives are an arm-to-arm comparison of the following:

1. RECIST response to include
 - a. Overall Response Rate (ORR) as measured by RECIST v1.1 criteria
 - b. Disease control rate (DCR) as measured by RECIST v1.1 criteria
2. Time to a first symptomatic skeletal event (SSE)

2.1.3 Additional secondary objectives

1. Safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Periodic assessment of health-related quality of life to evaluate impact of intervention on patient well-being (HRQoL; EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF])
3. Health Economics
4. Progression-free survival (PFS) (radiographic, clinical, or PSA progression-free survival)
5. Biochemical response as measured by PSA. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG (sub-study of approximately 30 patients).

2.2 Trial endpoints

2.2.1 Alternate Primary endpoint

rPFS and OS are designated as alternate primary endpoints. rPFS is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. OS is defined as the time from randomization to the date of death from any cause.

rPFS will be assessed locally by each site. Additionally, patient scans will be collected for independent central review. The independent central review will be used to support the primary rPFS analysis. The local rPFS assessment will be supportive.

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Alpha allocation and recycling is used to ensure control of the overall Type I error rate.

2.2.2 Key Secondary endpoints

The key secondary endpoints include the following:

1. RECIST response to include:
 - a. Objective response rate (ORR) (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
 - b. Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
2. The time to a first SSE defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.

2.2.3 Additional Secondary endpoints

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be reported using the EuroQol 5-dimensions 5-level [EQ-5D-5L] questionnaire, Functional Assessment of Cancer Therapy – Prostate [FACT-P] questionnaire and Brief Pain Inventory – Short Form [BPI-SF]
3. Health economics
4. Progression-free survival is defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
 - a. Radiographic progression is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 (PCWG3) Guidelines.
 - b. Unequivocal clinical progression. Unequivocal evidence of clinical progression is defined as:
 - Marked escalation in cancer related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
 - Immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression

- Marked deterioration in ECOG performance status to \geq Grade 3 and/or in the opinion of the investigator ECOG deterioration indicates clinical progression
 - In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression
 - c. PSA progression is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
 6. Dosimetry, PK, and ECG in a sub-study of approximately 30 patients

3. TRIAL DESIGN

3.1 Overview of the clinical trial design

This is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu -PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive/best standard of care as compared to best supportive/best standard of care alone ([Figure 1](#)).

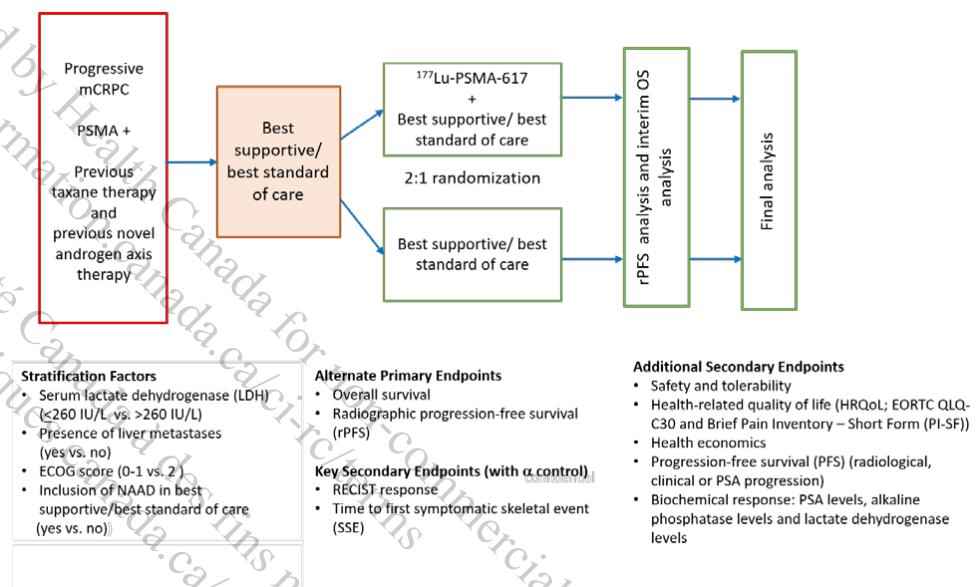


Figure 1 Diagram of trial design

ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castration-resistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Best supportive/best standard of care includes available care for the eligible patient according to best institutional practice and at the discretion of the investigator. Novel androgen axis drugs [NAADs] (i.e., enzalutamide or abiraterone) are allowed.

Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment may not be administered on study.

At screening, potential subjects will be assessed for eligibility and will undergo a ^{68}Ga -PSMA-11 PET/computed tomography (CT) scan to evaluate PSMA positivity. Only patients with PSMA-positive cancer will be randomized in a 2:1 ratio to receive either ^{177}Lu -PSMA-617 plus best supportive/best standard of care (investigational arm) or to receive best supportive/best standard of care alone (BS/BSC-only arm). Randomization will be stratified by 4 factors (Section 3.4.3).

Patients randomized to the investigational arm must begin ^{177}Lu -PSMA-617 dosing within 28 days after randomization. These patients will receive best supportive/best standard of care and 7.4 GBq ($\pm 10\%$) ^{177}Lu -PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After the Cycle 4 dose of ^{177}Lu -PSMA and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- Has shown good tolerance to the ¹⁷⁷Lu-PSMA-617 treatment.

If the patient meets all of the criteria above and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet any of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

Best supportive/best standard of care for each patient will be selected at the discretion of the patient's physician, prior to randomization and will be administered per the physician's orders and continued until the patient comes off the treatment part of the study and enters the long-term follow-up stage.

A patient may choose to discontinue randomized treatment part of the study at any time. If a patient chooses only to discontinue from the randomized treatment in the study for a reason other than radiographic progression, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS, and survival follow-up. The patient will continue to be followed for long term follow up unless they specifically withdraw consent from long term follow-up of the study. An End of Treatment (EOT) visit should occur once a patient discontinues randomised treatment for any reason (patient or investigator decision, going on to long term follow up, etc.).

The EOT visit should occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

If a patient discontinues randomized treatment for any reason other than radiographic progression, they will be asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS.

After the EOT visit, patients will enter the long-term follow-up period. The long-term follow-up period will include the collection of rPFS (if discontinuing for reasons other than radiographic progression), survival and information about new treatments, along with the patient's response to these treatments, adverse events assessment, and results of hematology and chemistry testing. During follow-up, patients will be followed for safety and survival. They will be contacted every 3 months (\pm 1 month) via phone, email, or letter for 24 months or until 508 deaths have occurred.

Patients who withdraw their consent to participate in the study for any reason other than radiographic disease progression will be asked for permission to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

Page 26 of 104

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

This study will enroll approximately 814 patients involving about 110 sites worldwide.

3.1.1 Study design update

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events, an interim analysis of OS, to be conducted contemporaneously with the primary analysis of rPFS, and a final analysis of OS with 489 deaths.

However, shortly after commencement of the trial, a high, early dropout rate amongst those randomized to BS/BSC only became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued. At time of the rPFS primary analysis, there will also be an interim analysis of OS; this OS analysis will be on an intent to treat (ITT) basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT analysis of the OS primary objective will be performed when 508 deaths have accrued. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

3.1.2 Study design update – Dosimetry, PK and ECG sub-study

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

In order to not bias the results obtained from randomized patients in the main study, the data of the sub-study patients will be analyzed descriptively and not considered in the primary and secondary analysis of the main study. The sub-study details and analyses will be presented in a separate report. Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific tests conducted in the sub-study, as described in Appendix 12, and the separate sub-study manual, the treatment regimen and patient care management remain identical to that implemented in the main study.

3.2 Rationale for the study design

The primary objective of this study is to compare the two alternate endpoints of rPFS and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to best supportive/standard of care versus patients treated by best supportive/best standard of care alone. The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS **or** OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study. Secondary endpoints have been defined by PCWG3 as well as FDA and EMEA guidance. In view of the highly symptomatic nature of advanced mCRPC both validated pain (BPI-SF) and HRQoL (EQ-5D-5L and FACT-P) measurements will be collected using various questionnaires.

3.3 Measures taken to minimize/avoid bias

Patients will be randomized to 1 of 2 treatment arms, with exception to the additional 30 patients in the sub-study who will receive the investigational treatment. Randomization will be stratified to avoid bias in treatment selection (Section 3.4.3). Treatment will be open-label.

Reading of the baseline ⁶⁸Ga-PSMA-11 PET/CT scan will be done by central readers for consistency.

3.4 Description of the clinical trial

3.4.1 Description of investigational medicinal product

The ⁶⁸Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi). For background and additional details on ⁶⁸Ga-PSMA-11, refer to the ⁶⁸Ga-PSMA-11 Investigator's Brochure.

Refer to the Fendler et al 2017 publication “⁶⁸Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0 guideline” for an overview of ⁶⁸Ga-PSMA-11 recommendations. Details of the patient preparation and administration can be found in the Imaging Manual.

The ¹⁷⁷Lu-PSMA-617 solution for injection consists of a sterile solution in glass vials containing 7.4 (± 0.74) GBq of ¹⁷⁷Lu-PSMA-617 at time of injection.

Refer to the ¹⁷⁷Lu-PSMA-617 IB for additional details of the investigational medicinal product including the pharmacological class and action, the dosage form including excipients, and any available packaging and labelling.

3.4.2 Dosage and rationale for dose selection

In the investigational arm, patients will receive best supportive/best standard of care regimen and IV 7.4 GBq ($\pm 10\%$) ¹⁷⁷Lu-PSMA-617 once every 6 weeks (± 1 week) for a maximum of 6 cycles.

After 4 cycles patients will be reassessed to determine if a further 2 cycles can be given for a maximum of 6 cycles (Section 3.1).

The basic principle of ^{177}Lu -PSMA-617 radioligand therapy is to systemically deliver low dose rate radiation specifically to multiple PSMA positive prostate cancer lesions, while sparing normal tissues. To date, 11 dosimetry studies have been conducted and published in over 100 patients. The results are consistent across the studies, and demonstrate exposure that correlates well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted radionuclide. The primary sites of non-tumor uptake were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms contributing to exposure in the kidneys where approximately 50% of the injected dose is cleared within 48 hours (Kratochwil et al 2016). PSMA-negative tissues like the bone marrow, are exposed transiently to ^{177}Lu -PSMA-617 while in circulation, however this exposure is minimized due to its rapid elimination.

^{177}Lu -PSMA-617 is well tolerated according to the clinical experience that has been documented in 24 publications, summarizing the safety and or efficacy information from over 500 subjects. Across these studies doses have ranged from 2.0-9.3 GBq, and schedules have typically followed an administration schedule of once every 4 to 12 weeks, for 1-8 cycles. The majority of these publications have used a regimen of 4 cycles of 6 GBq every 8 weeks, as published by the German Radiopharmaceutical Society in 2015. However efficacy and safety information from the prospective phase 2 study suggested that dosing of 6-8 GBq every 6 weeks for 4 cycles was well tolerated and efficacious (Hofman et al 2018).

Clinical series now show reports of more than 4 cycles of ^{177}Lu PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018). In addition, a recent review suggests optimal dosing of 6 cycles of ^{177}Lu -PSMA-617 administered every 6 weeks in a decreasing scale reaching a total cumulative absorbed dose of 44 GBq (Emmett et al 2017). Six fractions of 7.4 GBq, delivers a similar total dose of 44.4 GBq.

In the ANZUP1603 study in 200 Australian patients (NCT03392428), which is comparing ^{177}Lu -PSMA-617 with cabazitaxel, the dose starts at 8.5 GBq ^{177}Lu -PSMA-617 and reduces by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, 6 (cycle #6). A maximum of 6 cycles given every 6 weeks is what is being evaluated, which equates to a cumulative dose that is similar to that for this proposed study.

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu -PSMA-617 administration in this clinical trial.

3.4.3 Subject allocation to treatment

Patients will be randomized by an interactive response system in a 2:1 ratio to the investigational treatment arm or the best supportive/best standard of care-only arm using a permuted block scheme. Patients included in the sub-study will not undergo randomization as all patients will receive the investigational arm.

Randomization will be stratified by the following factors:

- LDH (\leq 260 IU/L vs. $>$ 260 IU/L)
- Presence of liver metastases (yes vs. no)
- ECOG score (0 or 1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs no)

3.4.4 End of treatment visit

An EOT visit should occur once a patient discontinues the treatment part of the study for any reason (patient or investigator decision, going on to long term follow up, etc.).

This visit should occur approximately 30 days from the last dose of ^{177}Lu -PSMA-617 or the date of the best supportive/best standard of care end of treatment decision (whichever occurs later), but before the initiation of subsequent anti-cancer treatment, outside of what is allowed on study.

3.4.5 Duration of Subject Participation

Patients may continue treatment until radiographic progressive disease, withdrawal of consent, the occurrence of unacceptable toxicity, or a determination by the investigator the patient is not clinically benefiting. As per the patient's physician, when the participant requires care that is not allowed on study, the participant will discontinue treatment and enter the long-term follow-up period. While the patient and/or physician may decide prematurely to cease taking randomized therapy at any time, full follow-up of all randomized patients for the intended duration of the trial is planned by design for the collection of rPFS and OS data.

It is anticipated that it will take approximately 14 months to randomize the required 814 patients in the study. After the last patient is randomized, patients will be followed for up to 24 months or at least until 508 deaths have occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be approximately 38 months.

3.5 End of trial definition

The trial and long-term follow-up procedures are expected to continue at least until 508 deaths have occurred. For timing of the rPFS and OS analyses and any rules for early statistical curtailment, refer to Section 8.1.

4. SELECTION AND DISCONTINUATION OF SUBJECTS

Written informed consent must be obtained prior to any study-related procedures. The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. While full follow-up is intended in the ITT population for the planned duration of the trial, participants must also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. A copy of the signed written informed consent form (ICF) will be given to the participant for their review and signature.

4.1 Inclusion criteria

To qualify for enrollment, patients must meet the following criteria:

1. Patients must have the ability to understand and sign an approved ICF.
2. Patients must have the ability to understand and comply with all protocol requirements.
3. Patients must be ≥ 18 years of age.
4. Patients must have an ECOG performance status of 0 to 2.
5. Patients must have a life expectancy >6 months.
6. Patients must have histological, pathological, and/or cytological confirmation of prostate cancer.
7. Patients must have a positive ^{68}Ga -PSMA-11 PET/CT scan, as determined by the sponsor's central reader.
8. Patients must have a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
9. Patients must have received at least one NAAD (such as enzalutamide and/or abiraterone).
10. Patients must have been previously treated with at least 1, but no more than 2 previous taxane regimens. A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane. If a patient has received only 1 taxane regimen, the patient is eligible if:
 - a. The patient's physician deems him unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation or intolerance, etc.).
11. Patients must have progressive mCRPC. Documented progressive mCRPC will be based on at least 1 of the following criteria:
 - a. Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL.
 - b. Soft-tissue progression defined as an increase $\geq 20\%$ in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions.
 - c. Progression of bone disease: evaluable disease or new bone lesion(s) by bone scan (2+2 PCWG3 criteria, [Scher et al 2016](#)).
12. Patients must have ≥ 1 metastatic lesion that is present on baseline CT, MRI, or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.
13. Patients must have recovered to \leq Grade 2 from all clinically significant toxicities related to prior therapies (i.e. prior chemotherapy, radiation, immunotherapy, etc.).

14. Patients must have adequate organ function:

a. Bone marrow reserve:

- White blood cell (WBC) count $\geq 2.5 \times 10^9/L$ ($2.5 \times 10^9/L$ is equivalent to $2.5 \times 10^3/\mu L$ and $2.5 \times K/\mu L$ and $2.5 \times 10^3/\text{cumm}$ and $2500/\mu L$) OR absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ ($1.5 \times 10^9/L$ is equivalent to $1.5 \times 10^3/\mu L$ and $1.5 \times K/\mu L$ and $1.5 \times 10^3/\text{cumm}$ and $1500/\mu L$)
- Platelets $\geq 100 \times 10^9/L$ ($100 \times 10^9/L$ is equivalent to $100 \times 10^3/\mu L$ and $100 \times K/\mu L$ and $100 \times 10^3/\text{cumm}$ and $100,000/\mu L$)
- Hemoglobin $\geq 9 \text{ g/dL}$ (9 g/dL is equivalent to 90 g/L and 5.59 mmol/L)

b. Hepatic:

- Total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (ULN). For patients with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for patients with liver metastases

c. Renal:

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq 50 \text{ mL/min}$

15. Albumin $> 3.0 \text{ g/dL}$ (3.0 g/dL is equivalent to 30 g/L).

16. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible.

17. HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes are included in this trial.

18. For patients who have partners of childbearing potential: Partner and/or patient must use a method of birth control with adequate barrier protection, deemed acceptable by the principle investigator during the study and for 3 months after last study drug administration.

19. The best standard of care/ best supportive care options planned for this patient:

- Are allowed by the protocol.
- Have been agreed to by the treating investigator and patient.
- Allow for the management of the patient without $^{177}\text{Lu-PSMA-617}$.

4.2 Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation. Previous PSMA-targeted radioligand therapy is not allowed.
2. Any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy [including monoclonal antibodies]) within 28 days prior to day of randomization.
3. Any investigational agents within 28 days prior to day of randomization.
4. Known hypersensitivity to the components of the study therapy or its analogs.
5. Other concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, or investigational therapy.
6. Transfusion for the sole purpose of making a subject eligible for study inclusion.
7. Patients with a history of CNS metastases must have received therapy (surgery, radiotherapy, gamma knife) and be neurologically stable, asymptomatic, and not receiving corticosteroids for the purposes of maintaining neurologic integrity. Patients with epidural disease, canal disease and prior cord involvement are eligible if those areas have been treated, are stable, and not neurologically impaired. For patients with parenchymal CNS metastasis (or a history of CNS metastasis), baseline and subsequent radiological imaging must include evaluation of the brain (MRI preferred or CT with contrast).
8. A superscan as seen in the baseline bone scan.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
11. Diagnosed with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, patients with a prior history of malignancy that has been adequately treated and who have been disease free for more than 3 years are eligible, as are patients with adequately treated non-melanoma skin cancer, superficial bladder cancer.

4.3 Subject withdrawal of consent for study or treatment

A patient may choose to withdraw his consent for participation in the study at any time. If a patient chooses only to discontinue from the treatment arm in the study, the patient will be asked to confirm if they consent to continue to be followed for long-term safety, rPFS (if discontinuing for reasons other than radiographic progression), and survival follow-up. This may include blood work results, radiographic follow up and information about new treatments and his response to

these treatments. Patients may also choose to be followed for survival only long-term follow up. This trial design is ITT so that all subjects are to be followed for up to 24 months for safety and survival or until 508 deaths have occurred. The total of 508 deaths are expected to have occurred approximately 13 months after the last patient has been randomized.

5. TREATMENT OF SUBJECTS

5.1 Treatment with the investigational medicinal product

5.1.1 Administration of ^{68}Ga -PSMA-11

For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure. The ^{68}Ga -PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 111 - 185 MBq (3 - 5 mCi).

5.1.2 Administration of ^{177}Lu -PSMA-617

Once every 6-weeks (\pm 1 week), 7.4 GBq (\pm 10%) ^{177}Lu -PSMA-617 will be administered. A 7.4 GBq dose is equivalent to 200 mCi or 7400 MBq.

Treatment with ^{177}Lu -PSMA-617 must be performed in accordance with national and/or local radiation and safety requirements.

A saline flush with \geq 10 mL of normal saline must be administered to ensure patency of the intravenous line before administering with ^{177}Lu -PSMA-617 administration.

^{177}Lu -PSMA-617 will be administered slowly by intravenous route and followed by a saline flush. The time of administration must be recorded. The total activity administered must be measured (GBq).

Vital signs will be collected 15(\pm 5) minutes before and at 30(\pm 5) and 60(\pm 5) minutes following administration.

Patients should also be monitored for any evidence of pain or burning sensation during the injection. Patients should be encouraged to maintain a good fluid intake on the day of treatment and following therapy.

Date and time of patient discharge following ^{177}Lu -PSMA-617 administration should be recorded.

A decision to order ^{177}Lu -PSMA-617 should be communicated to the sponsor or designee no later than 10 business days prior to the planned administration for each cycle.

5.1.3 Toxicity risk reduction and supportive care for ^{177}Lu -PSMA-617 injections

Supportive care should be provided as deemed necessary by the treating physician.

Oral hygiene

Patients should be advised to use sodium bicarbonate mouthwash during the first 3 days of each cycle.

Nausea and vomiting

Mild nausea and vomiting may occur without prophylactic therapy and antiemetic treatment is recommended. Oral or IV ondansetron (or equivalent) and/or dexamethasone or equivalent institutional anti-emetic regimen should be administered on the day of ^{177}Lu -PSMA-617 administration. If oral administration is given, it should occur at least 30 minutes before dosing and, if by injection, at least 15 minutes prior to infusing ^{177}Lu -PSMA-617.

Additionally, dexamethasone and domperidone/metoclopramide or institutional anti-emetic regimen may be administered on Days 2 and 3 of each cycle if required at the discretion of the investigator.

Other anti-emetics should be used as required as per standard clinical practice.

Additional suggested treatment guidelines

A listing of additional suggested treatment guidelines can be found in [Appendix 2](#). These are to be used at the discretion of the investigator.

5.1.4 Management of toxicity adverse events: dosing delays and modification

Within the first few days of treatment the most common adverse events (AEs) are general fatigue and an increase in bone pain. Symptomatic hematologic toxicity may occur but is not common.

Every effort should be made to keep the treatment cycle of 6 weeks (± 1 week) at the prescribed doses. Physical exams, assessment of toxicities, along with hematology and chemistry results must all be assessed prior to dosing with ^{177}Lu -PSMA-617. At the discretion of the investigator, a dose of ^{177}Lu -PSMA-617 may be delayed or reduced. [Table 1](#) provides dose modification recommendations. Only one reduction in administered activity is permitted. If a patient has further toxicity that would require an additional reduction in administered activity, treatment with ^{177}Lu -PSMA-617 must be discontinued. Once a dose is reduced, treatment with ^{177}Lu -PSMA-617 should not be re-escalated.

If a treatment delay due to adverse event or toxicity management persists for >4 weeks, treatment with ^{177}Lu -PSMA-617 must be discontinued. If treatment with ^{177}Lu -PSMA-617 is discontinued due to an AE, abnormal laboratory value, or toxicity, treatment with best supportive/best standard of care may continue at the discretion of the investigator if the patient has not radiographically progressed as measured by PCWG3 criteria.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Anemia, leukopenia, or neutropenia: <ul style="list-style-type: none">• Hemoglobin <10 g/dL• WBC count $<3.0 \times 10^9/\text{L}$• ANC $<1.5 \times 10^9/\text{L}$	\geq Grade 2	Hold ^{177}Lu -PSMA-617 administration until improvement to Grade 1 or baseline. Manage as deemed appropriate by investigator. The use of growth factors is permitted but should be discontinued once the AE resolves to Grade 1 or baseline. Checking hematologic levels (iron, B12, and folate) and providing supplementation is advocated. Transfusions may be given as clinically indicated for anemia.

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
Thrombocytopenia (platelet count of < 75 x 10 ⁹ /L)	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until improvement to Grade 1 or baseline. Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle. Transfusions may be given as clinically indicated for thrombocytopenia.
Non-platelet hematological toxicity (except lymphocytopenia that responds to medical intervention)	Grade 3 or Grade 4	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Serum creatinine increased ≥40% from baseline AND calculated creatinine clearance decreased >40% from baseline		Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Salivary gland toxicity	≥ Grade 2	Reduce ¹⁷⁷ Lu-PSMA-617 dose by 20% on the next cycle
Non-hematological, clinically significant toxicity not otherwise stated	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Electrolyte or metabolic abnormalities that are correctable within a 48 hr period without sequela	≥ Grade 2	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 1 or baseline
Gastrointestinal toxicity	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Fatigue	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Pain	≥ Grade 3	Hold ¹⁷⁷ Lu-PSMA-617 administration until resolved to Grade 2 or baseline
Spinal cord compression		Hold ¹⁷⁷ Lu-PSMA-617 administration until the compression has been adequately treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
Fracture in weight bearing bones		Hold ¹⁷⁷ Lu-PSMA-617 administration until fracture is adequately stabilized/treated and hematological parameters have returned to Grade 1 or baseline and ECOG performance status has returned to baseline at the time the next cycle administration is due
AST or ALT >5 × ULN in the absence of liver metastases		Discontinue ¹⁷⁷ Lu-PSMA-617
Renal toxicity	≥ Grade 3	Discontinue ¹⁷⁷ Lu-PSMA-617
Any serious AE that requires drug discontinuation or treatment delay of >4 weeks		Discontinue ¹⁷⁷ Lu-PSMA-617
Any unacceptable toxicity		Discontinue ¹⁷⁷ Lu-PSMA-617

Table 1 Toxicity management and dose modification recommendations

Event	Grade	Management recommendations
-------	-------	----------------------------

Note: Hematologic parameters (i.e., CBC with differential analysis) will be monitored every week in Cycle 1 only. Cycles 2 to 6, it will be monitored every 2 weeks. After Cycle 6, it will be monitored every 8 weeks.
AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECOG = Eastern Cooperative Oncology Group; Lu = Lutetium; PSMA = prostate-specific membrane antigen; ULN = upper limit of normal; WBC = white blood cell

5.2 Best supportive/best standard of care

The care of cancer patients must include cancer specialists accomplished in the care of patients with advanced prostate cancer, (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

The best supportive/best standard of care for the patient in either arm will be administered as per physician's orders and protocol at the institution and whenever feasible, best supportive/best standard of care should be optimized for all study participants prior to randomization. Patients will continue to be treated with best supportive/best standard of care until they require a treatment regimen not allowed on this study or have radiographic progressive disease as measured by PCWG3 criteria.

Other treatments for prostate cancer, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the investigator. These may include, but are not limited, to any of the interventions mentioned below.

Supportive measures (pain meds, hydration, transfusions, etc.), and ketoconazole are allowed on study.

Hormonal agents (single or combinations), estrogens including diethylstilbestrol (DES) and estradiol are allowed on study.

Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists are allowed on study.

Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride is allowed on study.

Abiraterone, enzalutamide, apalutamide or any other NAAD is allowed on study.

Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but no systemic radiopharmaceuticals. Y90 beads are allowed for approaches to liver metastasis as they are FDA approved.

Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates are allowed on study.

It is important to recognize that combinations of any, and all, of the above are allowed on the study and can be modified over time as needed.

5.3 Concomitant medications/ supportive care

5.3.1 Permitted concomitant medications/ supportive care

Consideration should be given to using concomitant bone health agents such as bisphosphonates on either arm of the study. Patients receiving bisphosphonates, denosumab, zoledronic acid or similar therapy prior to randomization may be maintained on this therapy during the study. Bisphosphonates denosumab, zoledronic acid or similar therapy can be stopped or started at the discretion of the investigator throughout the study.

Patients must maintain castrate levels of serum/plasma testosterone either by chemical castration or by having had an orchectomy.

Medications for myelosuppression

Blood transfusion or erythropoietin stimulation agents are allowed throughout the study after randomization. Routine prophylaxis with GCSF/granulocyte-macrophage colony-stimulating factor and erythropoietin is not recommended. Nevertheless, use is permitted at the investigator's discretion.

Refer to Section 5.1.4 for guidance on the management of toxicity.

5.3.2 Prohibited concomitant medications

Investigational agents, cytotoxic chemotherapy, immunotherapy, or other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment may not be administered on study.

5.4 Monitoring treatment compliance

The investigational medicinal product will be administered only at the investigational site under the direction of the investigator. Compliance with ¹⁷⁷Lu-PSMA-617 therapy will be monitored and ensured.

5.5 Treatment discontinuation

Patients may discontinue the treatment part of the study for any of the following reasons:

- Evidence of tumor progression by radiological assessment as measured by PCWG3 criteria
- Unacceptable toxicity
- Patient non-compliance or voluntary withdrawal
- Required use of a prohibited treatment
- Evidence that the patient is no longer clinically benefiting
- At the sponsor's or investigator's discretion

Patients that discontinue treatment due to unacceptable toxicity should return to the clinic for the End of Treatment visit. Participants who discontinue ¹⁷⁷Lu-PSMA-617 due to unacceptable toxicity may continue to receive best supportive/best standard of care alone during the treatment part of the study until they discontinue the treatment part of the study and enter long term follow up.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1 Screening procedures and baseline assessments

Screening procedures and baseline assessments will be performed within 4 weeks of randomization (enrollment for sub-study patients) except for baseline imaging. Any procedure or assessment done within this time frame may be accepted as the baseline procedure or assessment. Baseline medical imaging (CT with contrast/ MRI, and bone scan) is to be performed within 28 days of start of treatment. Any medical imaging done within this time frame may be accepted as the baseline imaging. The screening procedures are detailed in [Table 2](#).

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Informed consent	As per local/central IRB/IEC/REB timing requirements but prior to the performance of any study specific procedures.
Adverse Event (AE) monitoring and Serious Adverse Event (SAE) reporting	Begins at time of consent.
Inclusion/exclusion criteria	Refer to Section 4.1 and Section 4.2 for additional details.
Medical history	Collect medical history, including the following details about prior prostate cancer treatment(s): <ul style="list-style-type: none">• Date of initial diagnosis• Approximate start and stop date of each therapy• Date and type of progression (e.g. PSA, radiological, bone, or no clinical benefit)• Site of progression (new lesions, existing lesions, or both) when available
Prior/concomitant medication review	
Full physical examination	Should be performed by a qualified medical practitioner.
Height	
Weight	
ECOG performance score	Refer to Appendix 4 for the ECOG performance score scale.
Vital signs	Includes: blood pressure, pulse, and respiratory rate

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
CT with contrast/MRI	CT with contrast /MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.
^{99m} Tc diphosphonate bone scan	Baseline and follow up radiological disease assessments must include bone scans performed with technetium-99m labeled diphosphonates as per the local standard of care for patients with prostate cancer. Use the PCCTC bone scan assessment tool to document lesions (included in Appendix 11).
Histology	Pathology report of the most recent biopsy required at enrollment.
Disease pattern	Bone, visceral, soft tissue, and lymph nodes
12-lead ECG	
Hematology	Refer to Section 6.3.1 for list of tests
Chemistry	Refer to Section 6.3.1 for list of tests
Urinalysis, macroscopic (microscopic when indicated)	Refer to Section 6.3.1 for list of tests
Serum testosterone	
PSA	Includes PSA results and dates of 2 previous measurements. Prior measurements are needed to assess PSA velocity/doubling time.
BPI-SF, EQ-5D-5L and FACT-P	Baseline pain score assessment (BPI-SF) and HRQoL (EQ-5D-5L, FACT-P) assessments. HRQoL assessments may be either self-completed by the subject, or administered via face-to-face interview and completed by a caretaker/clinician.
Best supportive/best standard of care determination	To be decided prior to randomization, as part of screening.
PSMA PET/CT scan	To be done once all other eligibility requirements are confirmed. The metastatic lesion requirement may be confirmed at the same time as the baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan. Baseline ⁶⁸ Ga-PSMA-11 PET/CT ^a scan must be done within 4 weeks of start of treatment but not within the 6 days prior to start of treatment. PSMA eligibility will be determined by central readers.
Screening registration	Initial screening registration should take place after the patient has signed the Informed Consent Form. It should be completed once all screening assessments have been completed and results confirmed except for metastatic lesion requirement and PSMA positivity.

Table 2 Screening procedures and baseline assessments

Screening Procedure or Baseline Assessment	Notes
Study enrollment	Study enrollment should take place after screening registration is completed and once the metastatic lesion requirement is confirmed by the site and PSMA positivity has been confirmed by the central readers. Patients randomized to the investigational arm are to begin dosing with ^{177}Lu -PSMA-617 within 28 days after randomization.

^a For background and additional details on ^{68}Ga -PSMA-11, refer to the ^{68}Ga -PSMA-11 Investigator's Brochure.

BPI-SF = Brief Pain Inventory – Short Form; CT = computed tomography; ECG = electrocardiography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; HRQoL = Health-related quality of life; IEC = Independent Ethics Committee; IRB = Institutional Review Board; MRI = magnetic resonance imaging; PCCTC = Prostate Cancer Clinical Trials Consortium; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; REB = Research Ethics Board; RECIST = Response Evaluation Criteria in Solid Tumors;

6.2 Efficacy assessments

For the timing of efficacy assessments, refer to the schedule of assessments provided in [Appendix 1](#). The timing of the additional assessments for the sub-study are provided in [Appendix 12](#).

6.2.1 Radiographic imaging for tumor assessments

Radiologic assessment should follow PCWG3 guidelines. Periodic radiographic imaging will include both:

- CT with contrast/MRI imaging
- Bone scans with technetium-99m labeled diphosphonates

CT with contrast/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis.

Disease progression by bone scan will be defined as at least 2 new bone lesions at the first post-treatment scan, with at least two additional lesions on the next (confirmatory) scan (2+2 PCWG3 criteria, [Scher et al 2016](#)). For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (2+2 PCWG3 criteria). If the second scan confirms the metastases, then the date of progression is the date of the scan when the first 2 new metastases were documented.

6.2.2 Additional Imaging Analyses

The baseline eligibility ^{68}Ga -PSMA-11 scan data will be used for additional exploratory analyses. The ^{68}Ga -PSMA-11 PET/CT and corresponding diagnostic CT/MRI scans will be used in a retrospective Independent Review assessing inter-reviewer variability. The Independent Review will serve to evaluate the reading procedure for ^{68}Ga -PSMA-11 PET/CT scans by

assessing the variability and reproducibility of visual assessment. Visual assessment will be independently performed by three reviewers on ^{68}Ga -PSMA-11 PET/CT scans and corresponding diagnostic CT/MRI scans.

In addition, Quantitative Analysis will also be performed to assess tumor burden and tumor characteristics on ^{68}Ga -PSMA-11 PET/CT scans at the time of enrolment. The association of these baseline data with rPFS, OS, and other efficacy endpoints will be assessed in exploratory analyses.

An imaging charter will provide a detailed and expanded description of the planned analyses.

6.2.3 RECIST criteria

The responses of soft tissue, lymph node, and visceral lesions to treatment will be characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations (see [Appendix 6](#) and [Appendix 7](#)).

6.2.4 Symptomatic skeletal events

The time to the first SSE will measure the time to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain, whichever occurs first.

6.2.5 Pain score

Pain will be assessed using the BPI-SF.

The BPI-SF will be used as part of this study to assess the severity of pain and the impact of pain on daily functions. Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide ([Cleeland 2009](#)).

A copy of the BPI-SF questionnaire is provided in [Appendix 8](#).

6.2.6 Health-related quality of life

The ECOG Performance Status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in [Appendix 4](#).

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL. EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL ([Rabin 2001](#)). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal ([EuroQoL Group 1990](#)). This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort,

anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three ([EuroQoL Group 2015](#)). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about>.

A copy of the EQ-5D-5L questionnaire is provided in [Appendix 9](#)

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer patients. The FACT-P is made up of 2 parts: the FACT-G (general) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G (Functional Assessment of Cancer Therapy – General) questionnaire is one of the most widely used HRQoL instruments and measures HRQoL in four different domains: Physical well-being, Functional well-being, Emotional well-being, and Social/Family well-being ([Cella et al 1993](#)). The PCS is designed specifically to measure prostate cancer-specific quality of life. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as global quality of life score with higher scores representing better QoL. The FACT system has a number of advantages as a method of measuring QoL:

- Questionnaires have been developed to reflect patients' concerns
- Measurements are reliable, reproducible, and have been validated in numerous studies ([Cella et al 1993, Esper et al 1997](#))
- Available in over 45 different languages
- Designed for patient self-administration, but can also be administered by interview format ([Webster et al 2003](#))

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: <http://www.facit.org/FACITOrg/Questionnaires>.

A copy of the questionnaire (FACT-P version 4) is provided in [Appendix 10](#).

HRQoL will be periodically assessed at baseline, prior to administration of each cycle of ¹⁷⁷Lu-PSMA-617, and through the End of Treatment visit.

6.2.7 Health Economics

A health economics (HE) analysis will be performed. Core health resource use information will be collected, using case report forms (CRFs) on days in hospital and any outpatient visits. Data collected on concomitant medication may also be used in the economic analysis.

For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be assessed in terms of quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios. Quality adjustments will be based on patients' responses to the EQ-5D health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow-up as part of the QoL questionnaire.

6.2.8 Clinical progression

Clinical progression will be assessed by the investigator. The following criteria should be used to determine when a patient has met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that is assessed by the investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status to \geq Grade 3 and a finding of the investigator that the deterioration indicates clinical progression
- In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression

6.2.9 PSA levels

Local labs will measure PSA levels. Increases and decreases will be tracked to assess PSA responses as per PCWG3 ([Appendix 7](#)).

6.3 Safety assessments

6.3.1 Clinical laboratory evaluations

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing.

Chemistry, urinalysis, and hematology testing will include the following:

- | | | | |
|------------|--|--|---|
| Chemistry | <ul style="list-style-type: none">• sodium• potassium• total and direct bilirubin• ALP• AST• ALT | <ul style="list-style-type: none">• LDH• blood urea nitrogen• creatinine• uric acid• phosphorus• chloride | <ul style="list-style-type: none">• bicarbonate• calcium• glucose• total protein• albumin |
| Urinalysis | <ul style="list-style-type: none">• urine pH• protein content• specific gravity• appearance and color | <ul style="list-style-type: none">• glucose• ketones | |
| Hematology | <ul style="list-style-type: none">• complete blood count (white blood cell count and differential)• red blood cell count• hemoglobin• hematocrit• platelet count | | |

6.3.2 Vital signs

Blood pressure, pulse and respiratory rate will be assessed.

6.3.3 Electrocardiograms

A 12-lead ECG will be done at screening.

6.3.4 Birth Control

It is recommended that male patients who are sexually active practice an effective barrier method of birth control (e.g., condom and spermicidal jelly). Effective birth control methods should be used from day of the ⁶⁸Ga-PSMA-11 dose, throughout study treatment and for at least 3 months following the last dose of ¹⁷⁷Lu-PSMA-617.

6.4 End of treatment visit procedures

The assessments and procedures to be done at the EOT visit are defined in the Schedule of Assessments tables, provided in [Appendix 1](#).

6.5 Long-term follow-up procedures

A long-term follow-up period will collect long term follow-up specific self-reported AE assessments, rPFS (if discontinuing for reasons other than radiographic progression), survival and treatment updates from patients every 3 months (\pm 1 month) via phone, email, or letter. Hematology and chemistry blood work results will also be collected. Patients who withdraw their consent to participate in the treatment portion of the study or come off the treatment portion of the study for any reason other than radiographic disease progression will be asked for permission

to continue long-term status updates which may include, in addition to the above, collection of radiographic images (bone scans and CT scans and/or MRIs).

These patients will be asked to sign a separate consent detailing what kind of long term follow up assessments and study updates they will agree to. They will also be able to designate a contact person (i.e. study doctor, local doctor, friend or family member) who may be contacted on their behalf to obtain follow up status updates.

For any of these patients who are unable to sign the second consent (i.e. does not return to the site, etc.) every effort will be made to document the extent of long term follow up they will agree to. This will be documented in their source records.

7. ADVERSE EVENTS

7.1 Adverse event definitions

The following definitions comply with the ICH E2A guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, and the safety definitions of the World Health Organization (WHO) International Drug Monitoring Center.

Term	Definitions ^a
Adverse Event (AE)	<p>Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.</p>
Adverse Drug Reaction	For an investigational medicinal product all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
Serious Adverse Event (SAE) or Adverse Drug Reaction	A serious adverse event or reaction is any untoward medical occurrence that at any dose: <ul style="list-style-type: none">• results in death;• is life-threatening;• requires inpatient hospitalization or prolongation of existing hospitalization;• results in persistent or significant disability/incapacity; or• is a congenital anomaly/birth defect. <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.</p>
Unexpected Adverse Drug Reaction ^b	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., Investigator's Brochure for an unapproved investigational medicinal product).

^a ICH E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

^b Also referred to as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

AE = adverse event; SAE = serious adverse event

7.2 Evaluating and recording adverse events

All AEs will be graded according to CTCAE v5.0. All AE monitoring and SAE recording and reporting will begin at the time of consent and will continue up to and including 30 days after the last dose of ¹⁷⁷Lu-PSMA-617 or the date of best supportive/best standard of care end of treatment decision, whichever is later. For patients that are not randomized, AE monitoring will continue up to and including 6 days after administration of ⁶⁸Ga-PSMA-11.

All AEs and abnormal test findings, regardless of suspected causal relationship to ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617, will be recorded in the patients' case histories. For all AEs sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617. AEs or abnormal test findings felt to be associated with ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

The investigator will promptly review AEs and abnormal test findings to determine if: 1) the abnormal test finding should be classified as an AE; 2) there is a reasonable possibility that the AE was caused by ⁶⁸Ga-PSMA-11 and/or ¹⁷⁷Lu-PSMA-617; and 3) the AE meets the criteria for a serious adverse event (SAE). If the final determination of causality is "unknown and of questionable relationship to the study drug" the adverse event will be classified as associated with the use of the study drug for reporting purposes. If the final determination of causality is "unknown but not related to the study drug" the determination and rationale will be documented in the patient's case history.

7.3 Immediate Adverse Event Reporting

Endocyte will ensure that all relevant safety information as required by local and/or national laws, directives and/or regulations are reported to the appropriate Competent Authorities as well as the Principal Investigator and/or IRBs/Ethics Committees.

7.3.1 Serious Adverse Events

SAEs require expeditious handling and MUST IMMEDIATELY be reported upon discovery so the sponsor may comply with regulatory requirements.

Any SAE, regardless of causal relationship, must be reported to the Sponsor Contact listed in the Sponsor Contact section (Section 7.3.3) immediately (no later than 24 hours after the investigator becomes aware of the SAE) by emailing or faxing a completed SAE form to the number/email indicated and then confirming by telephone that the email/fax was received. Compliance with this time requirement is essential so that the sponsor may comply with its regulatory obligations.

Follow-up information relating to an SAE must be reported to the Sponsor Contact in Section 7.3.3 within 24 hours of receipt by the investigator by emailing or by faxing a completed SAE form to the number indicated and confirming by telephone that the fax was received. The patient should be observed and monitored carefully until the condition resolves or stabilizes or its cause is identified.

SAEs which are: 1) associated with ^{68}Ga -PSMA-11 and/or ^{177}Lu -PSMA-617; 2) fatal or life-threatening; and 3) unexpected, will be reported to the principal investigator and/or IRBs/Ethics Committee/Research Ethics Boards (REBs) and the Regulatory Authorities within 7 days of awareness of the respective information. Other SAEs which are: 1) associated with the investigational drug or study treatment; 2) non-fatal or non-life-threatening; and 3) unexpected will be reported to the principal investigator and/or IRBs/Ethics Committee/REBs and Regulatory Authorities within 15 days of awareness of the respective information.

7.3.2 Serious adverse event subject follow-up

Follow-up information to a reported SAE will be submitted to the principal investigator and/or IRBs/Ethics Committees and Competent Authorities in accordance with local regulations and international guidelines. If the results of the follow-up investigation show that an SAE that was initially determined to not require reporting does, in fact, meet the requirements for reporting, the investigator will report the SAE to the principal investigator and/or IRBs/Ethics Committees/REBs in accordance with local regulations and international guidelines.

7.3.3 Sponsor Contact Information for Immediate Reporting

Serious adverse events and follow-up information should be reported on a completed serious adverse event report form to PrimeVigilance by fax at +1 800 886 0743 or emailed to endocyte@primevigilance.com. If reported by fax, please confirm receipt of fax via phone call to PrimeVigilance at +44(0) 1483 566 462.

8. STATISTICS

This section outlines the general study design, study endpoints, and statistical analysis strategy for the study.

All statistical analyses will be carried out using SAS version 9.4 (or later). The SAP will be written and finalized prior to the first planned interim analysis and without knowledge of any by-treatment group accumulated data. The SAP will provide a detailed and expanded description of the statistical methods outlined in this protocol. Additional analyses, such as in important subgroups, will be described.

8.1 Revision to the protocol and statistical analyses of rPFS and OS

The trial was originally designed to randomize 750 patients, targeting the primary analysis of rPFS with 457 events with a 1-sided alpha level of 0.001, an interim analysis of OS with a 1-sided alpha level of 0.001, to be conducted contemporaneously with the primary analysis of rPFS, and a final primary analysis of OS with 489 deaths with a 1-sided alpha of 0.023.

However, shortly after commencement of the trial, a high early dropout rate amongst those randomized to BS/BSC-only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients which consequently could result in bias in the analysis of rPFS. Remedial measures to curtail this phenomenon were implemented and made effective on March 5th, 2019. As part of

the plan to address the early withdrawal of consent in the BS/BSC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after March 5th, 2019; therefore, rPFS will be analyzed in these patients once 364 events have accrued with a 1-sided alpha level of 0.004. At time of this rPFS primary analysis, there will be an interim analysis of OS with a 1-sided alpha level of 0.001; this OS analysis will be on an ITT basis and will include all randomized patients (i.e., including those randomized before March 5th, 2019). Following the analysis of rPFS and the interim analysis of OS, a final ITT primary analysis of OS will be performed when 508 deaths have accrued with a 1-sided alpha level of 0.020. To achieve these analyses, the total number of subjects randomized into the trial was increased from N=750 to N=814. The revisions described do not alter the hypothesized treatment effects for rPFS and OS upon which the study was originally powered.

8.2 Revisions to planned analyses

Subsequent to the protocol revision, if further changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be further amended (consistent with ICH Guideline E9). Any changes to exploratory or non- confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR). Any post hoc exploratory analyses will be clearly identified in the CSR. Full details will be in the SAP. Any deviations from the statistical plan will be described and justified in a protocol amendment and/or in the CSR.

8.3 Sample size and power determination

The sample size was determined based on the alternate primary endpoints of rPFS and overall survival. Planned enrollment for this study is approximately 814 subjects.

Under the null hypothesis for survival, median survival is assumed to be 10 months on ¹⁷⁷Lu PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median overall survival on active is assumed to be 13.7 months for a HR of 0.7306.

Under the null hypothesis for rPFS, median rPFS is assumed to be 4 months on ¹⁷⁷Lu-PSMA-617 and best supportive/best standard of care (active) for a hazard ratio (HR) of 1.00. Under the alternative hypothesis, median rPFS on active is assumed to be 6 months for a HR of 0.67.

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months is expected to yield 508 deaths. This number of events provides at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients are expected to be randomized or after 5 March 2019, these being the patients to be included in the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients are expected to yield 364 rPFS events which will be sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided alpha level of 0.004. At the time of this rPFS analysis, 341

deaths are expected amongst all randomized patients. These interim OS data will be analyzed with a 1-sided alpha level of 0.001. Central independent assessments will be used to determine rPFS events.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results:

- if $p < 0.004$ 1-sided is achieved for rPFS and $p < 0.001$ 1-sided, is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.025 1-sided.
- if $p < 0.004$ 1-sided is achieved for rPFS but $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will be 0.024 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS but $p < 0.001$ 1-sided is achieved for interim OS, then the alpha level for the final analysis of OS will be raised to 0.021 1-sided.
- if $p < 0.004$ 1-sided is not achieved for rPFS and $p < 0.001$ 1-sided is not achieved for interim OS, then the alpha level for the final analysis of OS will remain at 0.020 1-sided.

This design provides at least 90% power for OS and 84% power for rPFS; with an overall Type I error rate ≤ 0.025 1-sided.

The observed HRs that will meet $p < 0.004$ for rPFS and the interim analysis of OS are 0.745 and 0.701 respectively; and the observed HR that will meet $p < 0.020$ to $p < 0.025$ in the final analysis of OS are 0.824 to 0.823.

8.4 Analysis populations

Analysis datasets are defined as follows:

- **Full Analysis Set (FAS):** All randomized patients. OS will be assessed on an ITT basis and related data will be summarized by randomized treatment.
- **PFS Analysis Set (PFS-FAS):** All patients randomized on or after March 5th, 2019. The primary analysis of rPFS will be based on this dataset on an ITT basis and related data will be summarized by randomized treatment.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline. Soft tissue response as measured by RECIST will be assessed in this dataset.
- **Safety Analysis Dataset:** There will be two safety datasets
 - The subset of patients who received at least one dose of ⁶⁸Ga-PSMA-11.
 - The subset of patients in the FAS who received at least one dose of randomized therapy. Patient safety data in this dataset will be summarized by treatment received.

8.5 Demographics and baseline disease characteristics

Demographic and baseline disease characteristic data will be summarized in the FAS and PFS-FAS for each treatment with frequency distributions and/or descriptive statistics (mean, standard

Page 50 of 104

deviation, median, range, and/or relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

8.6 Patient disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. This will be done for the FAS and the PFS-FAS. If known, a reason for their discontinuation will be given. Reporting of patient disposition will include:

- A summary of data on patient discontinuation
- A summary of data on overall qualification status of all patients
- An account of all significant protocol deviations

All patients enrolled in the study will be accounted for in the summation. The number of patients who do not qualify for analysis, who die, or who discontinue before treatment begins, will be specified.

8.7 Efficacy analyses

8.7.1 Alternate primary endpoint analysis

8.7.1.1 rPFS

Radiographic progression-free survival (rPFS) is defined as the time from the date of randomization to the date of radiographic disease progression as outlined in Prostate Cancer Working Group 3 (PCWG3) Guidelines (Scher et al 2016) or death from any cause. rPFS as determined by the independent central assessment will be used for this analysis. PFS eventsThe primary analysis of rPFS will be based upon the PFS-FAS and will take place once 364 rPFS events have been reached. The allocated alpha level for the rPFS analysis is 0.004 1-sided.

Patients who are alive without radiographic progression at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for rPFS at the time of their last radiographic assessment or at the data cut-off date. rPFS data will be displayed using Kaplan Meier curves from which median rPFS times will be estimated for both treatment arms.

A stratified log-rank test model will be the primary statistical methodology used to analyze rPFS in the PFS-FAS dataset, stratified for the randomization stratification factors.

Supportive analyses of rPFS will be performed in terms of (i) a stratified Cox regression model on the PFS-FAS dataset with a single covariate for randomized treatment, and stratifying again for the randomization stratification factors; and (ii) the same as (i) but based upon the FAS dataset. The HR and CI from (i) will be used as an adjunct to the primary stratified log rank test p-value to provide the quantification of the treatment effect on rPFS.

8.7.1.2 OS

Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause and will be assessed in the FAS. A formal interim analysis of OS is planned to

occur at the time of the rPFS analysis (with 364 rPFS events in PFS-FAS); it is anticipated that approximately 341 deaths will have accrued in the FAS at the time of the rPFS analysis in the PFS-FAS. The allocated alpha level for OS in this interim analysis is 0.001 1-sided. The final analysis of OS is event driven and will take place once 508 deaths have occurred in the FAS. As described in Section 8.3, the allocated alpha level for the final OS analysis will be between 0.020 and 0.025 1-sided, depending on the results of the earlier primary rPFS analysis and interim OS analysis.

Patients who are lost to follow-up or are alive at the time of the OS analysis (for both interim and final analyses) will be censored at the time they were last known to be alive or at the date of event cut-off for the OS analysis. OS data will be displayed using Kaplan Meier curves from which median OS will be estimated for both treatment arms.

OS will be analyzed using the same statistical methodology as described for the primary analysis of rPFS. Supportive analyses of OS will be performed at the interim and final in terms of Cox regression model on the FAS dataset with a single covariate for randomized treatment, stratifying for the randomization stratification factors. The HR and CI from these analyses be used as an adjunct to the primary stratified log rank test p-values to provide the quantification of the treatment effect on OS.

8.7.1.3 Statistical Interpretation of Alternate Primary Endpoints

The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either the primary analysis of rPFS **or** OS at the respective allocated alpha level; it is **not required** to meet both rPFS and OS to be declared a statistically positive study.

Note, this applies to OS assessed at either the interim or the final analysis, i.e. for the study to be declared statistically positive requires rPFS to meet its allocated alpha level **or** OS to meet its allocated alpha level at **either** (i) the formal OS interim analysis (conducted at the time of the rPFS analysis) **or** (ii) at the final OS analysis with 508 deaths.

Alpha allocation and recycling are used to ensure control of the overall Type I error rate as described in Section 8.3.

8.7.2 Secondary efficacy analyses

Key secondary endpoints

Key secondary endpoints will be subject to Type I error control. These endpoints are:

1. RECIST ORR and DCR
2. Time to SSE

The primary evaluation of these endpoints will be assessed in the PFS-FAS dataset. Time to SSE will be analyzed using a Cox regression model with a single covariate for randomized treatment, stratifying for the randomization stratification factors. ORR and DCR will be analyzed using logistic regression with a single covariate for randomized treatment and stratification for the randomization stratification factors. The odds ratio (active: control), its 95% confidence interval

and associated 2-sided p-value will be presented. The DOR for binary response endpoint ORR will also be summarized and presented using Kaplan-Meier curves.

To control the overall Type I error rate, if either alternate primary endpoint is met, then the key secondary endpoints will be assessed using the Hochberg closed test procedure at the alpha level applicable to the successful alternate primary endpoint. This procedure is reasonable given the positive correlation between the two key secondary endpoints.

Supportive analyses of ORR, DCR and time to SSE will be performed in the FAS dataset using the same methods as described for the primary evaluation of these endpoints.

Additional Secondary Endpoints

Additional Secondary Endpoints will be assessed at the nominal 5% level, i.e. there will be no alpha control applied. These endpoints will be assessed in PFS-FAS with the exception of safety which will be assessed using the Safety analysis sets and are:

1. To evaluate the safety and tolerability of ¹⁷⁷Lu-PSMA-617
2. Aspects of HRQoL will be self-reported by patients (or via interview format) using the EQ-5D-5L and FACT-P questionnaires, and pain will be assessed by patients using the BPI-SF.
3. Health economics
4. PFS as defined as the date of randomization to the date of first evidence of radiographic progression, clinical progression, PSA progression, or death from any cause, whichever occurs first.
5. Biochemical response endpoints:
 - a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks.
 - b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
6. Dosimetry, PK and ECG in a sub-study of approximately 30 patients presented separately from the main study analyses.

Event-free survival endpoints (e.g., PFS, time to pain worsening) will be analyzed using a Cox regression model in the same manner as described for time to SSE except using a 2-sided p-value. DCR will be analyzed in the same manner as ORR and HRQoL will be analyzed in the same manner as pain score over time. Time to pain improvement response after initial pain worsening will be analyzed using mixture distribution methodology akin to that described by [Ellis et al 2008](#).

8.8 Safety analyses

All safety evaluations will be based on the Safety Analysis Set. The same analyses will be performed separately in the sub-study of approximately 30 patients.

8.8.1 Extent of exposure

The duration of exposure and dose intensity will be calculated. The relationship between dose intensity, duration of exposure, and frequency and severity of adverse events will be explored by data tabulation.

8.8.2 Analysis of adverse events

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A ⁶⁸Ga-PSMA-11 TEAE is defined as an AE that was not present prior to dosing with ⁶⁸Ga-PSMA-11 but appeared following dosing or was present at time of initial dosing but worsened during or after dosing. The treatment-emergent period will be defined as the period from the date of ⁶⁸Ga-PSMA-11 dosing up to 6 days after the date of ⁶⁸Ga-PSMA-11 dosing as long as prior to the first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the best supportive/best standard of care-only arm. Adverse events reported as “possibly”, “probably”, or “definitely” related to ⁶⁸Ga-PSMA-11 that occur beyond the 6-day reporting window but occur before the initiation of randomized treatment are also ⁶⁸Ga-PSMA-11 TEAEs. Unrelated ⁶⁸Ga-PSMA-11 adverse events that occur beyond 6 days will not be TEAEs.

A randomized treatment TEAE is defined as an AE that was not present prior to initiation of randomized treatment, defined as first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and Cycle 1 Day 1 for the BS/BSC arm, but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period from the initiation of randomized treatment up to 30 days after the date of the last dose or intervention of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

AEs leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

8.8.3 Analysis of laboratory assessments

Laboratory values and change from baseline will be summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented by treatment group. Subject listings of laboratory toxicities \geq Grade 3 will be provided.

8.8.4 Analysis of vital sign data

Vital sign data (observed and change from baseline) will be summarized using descriptive statistics by time point and treatment. Abnormal findings from physical examinations will be assessed for clinical significance which will be included in the AE listings and summaries.

8.9 IDMC and interim data evaluation

8.9.1 IDMC

An IDMC will be convened to review accumulating safety and safeguard patient interest in the study. Safety data monitoring will be conducted quarterly by the IDMC. These safety reviews will commence following the completion of the first three months of study accrual.

In addition, a summary of efficacy data will also be provided to the IDMC at the time of routine safety data reviews; these efficacy data will be provided for information only, no statistical analyses will be conducted. The only analyses of efficacy data are those formally planned for rPFS in the PFS-FAS at 364 events, interim OS (in the FAS) at the time of the rPFS analysis and final OS (in the FAS) with 508 deaths.

The IDMC will review these formal efficacy analyses. The IDMC may recommend early curtailment of trial on the basis of meeting one of the preplanned formal efficacy analyses or due to the emergence of an unforeseen safety concern placing patient safety at risk.

An IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis.

The IDMC can recommend a course of action, but the sponsor will make the final decision regarding whether or not to continue or stop the trial, based on any analysis for reasons related to safety or efficacy.

8.9.2 Formal interim analysis of OS

As described above in Section 8.3, one formal interim analysis is planned for OS in the FAS to take place at the time of the primary rPFS analysis in the PFS-FAS. The allocated alpha level for the interim OS analysis is 0.001 1-sided. Regardless of whether a positive result is attained at this time, for either rPFS or interim OS, patient follow-up will continue until 508 OS events have accrued in the FAS at which time a final OS analysis will be performed.

9. ACCESS TO SOURCE DATA/DOCUMENTS

During the course of the study, a representative of Endocyte or its designee will be contacting and/or visiting the study sites to monitor the progress of the study. Contacts with the investigator and on-site visits for the purpose of data audits, including the comparison of source documents with case report forms (CRFs) and study agent accountability logs, will occur. The principal investigator or his/her representative will need to be available to the representative of Endocyte or its designee during these visits.

Page 55 of 104

By signing the protocol, the investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, Endocyte, its designee, or responsible government agencies (as required by law) may review or copy source documents in order to verify case report form (CRF) data.

10. ETHICS

10.1 Institutional Review Board/Independent Ethics Committee/ Research Ethics Board (IRB/IEC/REB)

The investigator will obtain approval from the IRB/IEC/REB of the proposed clinical protocol and ICF for study recruitment and the approval will be provided to Endocyte or its designee prior to beginning the clinical trial. The only circumstance in which a deviation from the IRB/IEC/REB-approved clinical protocol/ICF may be initiated in the absence of prospective IRB/IEC approval is to eliminate an apparent immediate hazard to the research participants. In such circumstances, the investigator will promptly notify the IRB/IEC/REB of the deviation.

The investigator will promptly notify Endocyte of any regulatory inspection relating to this study, including either the institution or the IRB/IEC/REB, and will promptly provide Endocyte with a copy of any inspection report.

10.2 Informed consent

The investigator will make certain that an appropriate informed consent process is in place to ensure that potential participants, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research participants. The investigator, or his/her authorized designee, will obtain the written, signed ICF of each participant, or the participant's authorized representative, prior to performing any protocol-specific procedures on the participant. The date and time that the participant, or the participant's authorized representative, signs the ICF and a narrative of the issues discussed during the informed consent process will be documented in the participant's case history. The investigator will retain the original copy of the signed ICF, and a copy will be provided to the participant, or to the participant's authorized representative.

The investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled participants are adequately addressed and that the participants are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the investigator will obtain the informed consent of enrolled participants for continued participation in the clinical study.

10.3 Health Insurance Portability and Accountability Act

Preparation of the Health Insurance Portability and Accountability Act (HIPAA) authorization form is the responsibility of the investigator and must include all elements required by the United States (US) Department of Health and Human Service's Privacy Rule. Prior to the beginning of

Page 56 of 104

the study, the investigator must have the IRB or the appropriate institution privacy board's written approval/favorable opinion of the HIPAA authorization form.

The HIPAA authorization must be signed and personally dated by the participant or their legally acceptable representative and by the person who obtained the authorization.

For sites located outside of the US, local regulations regarding protection of individually identifiable health information must be followed.

10.4 Confidentiality

All records will be kept confidential and the participant's name will not be released at any time. Participant records will not be released to anyone other than Endocyte or its designee(s) and responsible government agencies. Data sets for each participant will be identified by a unique number. If participant records are sent to Endocyte or its affiliates or designees, the participant's name or other identifying information will be masked and participant registration number or other unique identifier substituted.

11. COMPLIANCE AND QUALITY CONTROL

Independent auditing of the clinical study for protocol and GCP compliance may be conducted periodically at selected clinical sites by the Endocyte, Inc. Quality Assurance.

The purpose of the sponsor's audit is to evaluate trial conduct and compliance with the protocol, standard operating procedures, GCP, and the applicable regulatory requirements.

Site monitoring visits will be conducted periodically at each clinical site. During site monitoring visits the following but not exhaustive list of points will be reviewed: patient informed consent, patient recruitment and follow-up, AE reporting including SAE documentation, outcome events documentation and reporting, investigational drug allocation, storage and accountability, concomitant therapy use, and quality of data.

11.1 Compliance with Monitoring and Audits

Representatives of Endocyte or its designee must be allowed to visit (scheduled in advance) all study site locations periodically to assess the data, quality, and study integrity. On site, they will review study records and directly compare them with CRFs and discuss the conduct of the study with the investigator and verify that the facilities remain acceptable. It is the responsibility of the investigator (or designee) to be present or available for consultation during such monitoring visits.

In addition, the study may be evaluated by Endocyte (or designee's) internal auditors and government inspectors who must be allowed access to CRFs, source documents, investigational medication records, and other study files. The sponsor's (or designee's) audit reports will be kept confidential to the extent permitted by law. The investigator must notify Endocyte promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to Endocyte. The investigator agrees to promptly take any reasonable steps that are

requested by Endocyte as a result of monitoring or auditing activities to address deficiencies in study conduct or documentation. In the event that Endocyte is unable to secure compliance with the Statement of investigator or study protocol and prematurely terminates a trial site, Endocyte will notify the FDA (as required by 21 CFR § 312.56) the site's IRB/IEC/REB, and other regulatory authorities, as required.

12. DATA HANDLING, RECORD KEEPING, AND COMPLIANCE

12.1 Investigational medicinal product accountability

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug destroyed.

12.2 Breaking the blind

Not applicable.

12.3 Data collection forms and source document identification

All source data will be retained by the trial site to ensure that, if requested, a monitor, auditor, or regulatory agency has access to the source documents.

Source data are the clinical findings and observations, laboratory and test data, and other information contained in source documents. Source documents are the original records (and certified copies of original records) including, but not limited to, hospital medical records, physician or office charts, physician or nursing notes, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, x-rays, biopsy reports, ultrasound reports, pharmacy records, or any other similar reports or records of any procedures performed in accordance with the protocol. Source documentation may also include any sponsor CRF when source data is recorded directly onto a CRF.

The health-related quality of life questionnaires will utilize electronic Clinical Outcome Assessments (eCOA) technology for direct entry of the patient's responses. The eCOA will serve as source data.

A CRF will be completed for each participant enrolled into the clinical study. Patients are to be identified by, year of birth, patient screening number and patient enrollment number. Information recorded on the CRF must match the source data recorded on the source documents.

The investigator will review, approve, and sign/date completed CRFs. Their signature serves as attestation ensuring that all clinical and laboratory data entered on the CRF are complete, accurate, and authentic. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the principal investigator. The transfer of duties must be recorded on the Delegation Log (kept on file at the site) and all sub-investigators must be listed on FDA Form 1572 or equivalent regulatory statement. The investigator must ensure that all sub-investigators are familiar with the protocol and all study-specific procedures and have appropriate knowledge of the study agent(s).

12.4 Record maintenance and retention

The investigator will maintain records in accordance with GCP guidelines including the following:

- IRB/IEC/REB correspondence (including approval notifications) related to the clinical protocol, including copies of adverse event reports and annual or interim reports
- All versions of the IRB/IEC/REB approved clinical protocol and corresponding ICFs and, if applicable, participant recruitment advertisements
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol and laboratory certification
- Instructions for on-site preparation and handling of the investigational drug, study treatment, and other study-related materials if not addressed in the clinical protocol;
- Participant screening and enrollment logs and signed ICFs
- Investigational drug accountability records, including documentation of drug return or destruction
- A summary of the final clinical study results

12.5 Archiving

Endocyte and the investigator will retain the records and reports associated with the clinical trial as required by local regulatory requirements after the marketing application is approved for the investigational drug. If a marketing application is not submitted or approved for the investigational drug the information will be retained until two years after investigations under the Investigational New Drug Application/Clinical Trial Application have been discontinued and the FDA/EMA/CA notified.

13. PUBLICATION POLICY

Endocyte and the investigators are committed to the publication and widespread dissemination of the results of this study. This study represents a joint effort between Endocyte and the investigators, and as such, the parties agree that the recommendation of any party concerning manuscripts or texts shall be taken into consideration in the preparation of final scientific documents for publication or presentation. All proposed publications and presentations by the investigators or their personnel and associates resulting from or relating to this study must be submitted to Endocyte for review 60 days before submission for publication or presentation.

If the proposed publication or presentation contains patentable patient matter, which, at Endocyte's sole discretion, warrants intellectual property protection, Endocyte may delay any publication or presentation for up to 60 days after approval for the purpose of pursuing such protection.

14. REFERENCES

Ahmazadehfar et al 2016

Ahmazadehfar H, Eppard E, Kürpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with ¹⁷⁷Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. *Oncotarget.* 2016;7(11):12477-88.

Ahmazadehfar et al 2015

Ahmazadehfar H, Rahbar K, Kürpig S, Bögemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with ¹⁷⁷Lu-DKFZ-617 PSMA of castrate-resistant metastatic prostate cancer: a two-centre study. *EJNMMI Research.* 2015;5:36.

Azad et al 2015

Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of Enzalutamide Following Abiraterone Acetate in Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer Patients. *European Urology* 2015; 67 23-29.

Badrising et al 2014

Badrising S, van der Noort V, van Oort IM, et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014; 120:968-75.

Benešová et al 2015

Benešová M, Schäfer M, Bauder-Wüst U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. *J Nucl Med.* 2015;56(6):914–20.

Brasso et al 2015

Brasso K, Thomsen FB, Schrader AJ, Schmid SC, Lorente D, Retz M, Merseburger AS, von Klot CA, Boegemann M, de Bono J. Enzalutamide Antitumour Activity Against Metastatic Castration-resistant Prostate Cancer Previously Treated with Docetaxel and Abiraterone: A Multicentre Analysis. *European urology.* 2015;68(2):317-24.

Bray et al 2012

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer.* 2013 Mar 1;132(5):1133-45. doi: 10.1002/ijc.27711. Epub 2012 Jul 26.

Bostwick et al 1998

Bostwick DG, Pacelli A, Blute M, Roche P, and Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. *Cancer.* 1998;82:2256-61.

Cella et al 1993

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993 Mar;11(3):570-9.

Cella et al 2009

Cella D, Nichol MB, Eton D, Nelson JB, Mulani P. Estimating clinically meaningful changes for the Functional Assessment of Cancer Therapy--Prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health.* 2009 Jan-Feb;12(1):124-9.

Cheng et al 2015

Cheng HH, Nadal R, Azad A, Gulati R, et al. Activity of enzalutamide in men with metastatic castration resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015; 18(2): 122–127. doi:10.1038/pcan.2014.53.

Cleeland 2009

Cleeland, CS. The Brief Pain Inventory User Guide. 2009. Available at: www.mdanderson.org/content/dam/mdanderson/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Das et al 2016

Das T, Guleria M, Parab A, Kale C, Shah H, Sarma HD, et al. Clinical translation of (177)Lu-labeled PSMA-617: Initial experience in prostate cancer patients. *Nucl Med Biol.* 2016; 43(5): 296–302.

Delker et al 2016

Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2016;43(1):42-51.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. *Contemp Clin Trials.* 2008 Jul;29(4):456-65.

Emmett et al 2017

Emmett L, Willowson K, Violet J, Shin J, Blanksby A, and Lee J. Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. *J Med Radiat Sci.* 2017 Mar; 64(1):52–60.

Esper et al 1997

Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology.* 1997 Dec;50(6):920-8.

EuroQoL Group 1990

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990 Dec;16(3):199-208.

EuroQoL Group 2015

EuroQol Group. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. April 2015, Version 2.1. Retrieved from https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Fendler et al 2017

Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Jun;44(6):1014-1024.

Ferdinandus et al 2017

Ferdinandus J, Eppard E, Gaertner FC, Kürpig S, Fimmers R, Yordanova A, et al. Predictors of Response to Radioligand Therapy of Metastatic Castrate-Resistant Prostate Cancer with 177Lu-PSMA-617. J Nucl Med. 2017 Feb;58(2):312-319.

Ferlay et al 2013

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on day/month/year.

Flaig et al 2016

Flaig TW, Potluri RC, Ng Y, Todd MB, and Mehra M. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182-91.

Ghosh and Heston 2004

Ghosh A and Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528-39.

Haberkorn et al 2016

Haberkorn U, Eder M, Kopka K, Babich JW, and Eisenhut M. New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. Clin Cancer Res. 2016 Jan 1;22(1):9-15.

Haug et al 2016

Haug AR, Shariat S, Eidherr H, Vraka C, Wadsak W, Mitterhauser M, et al. Initial experience with aggressive treatment of metastatic prostate cancer using 3 cycles of 7.4 GBq [177Lu]-PSMA every 4 weeks. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S212 EPW11.

Hillier et al 2009

Hillier SM, Maresca KP, Femia FJ, Marquis JC, Foss CA, Nguyen N, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17), 6932-40.

Hofman et al 2018

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, Iravani A, Kong G, Ravi Kumar A, Murphy DG, Eu P, Jackson P, Scalzo M, Williams SG, Sandhu S. [177Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018 Jun;19(6):825-833.

Hofman et al 2019

Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Iravani A, Kong G, Ravi Kumar A, Akhurst T, Mooi J, Guo C, Tran B, Jackson P, Scalzo m, Eu P, Williams S, Sandhu SK. Results of a 50 patient single-centre phase II prospective trial of Luteium-177 PSMA-617 theranostics in metastatic castrate-resistant prostate cancer. *J Clin Oncol.* 2019;37(suppl 7S): 228. Kirby et al 2011

Kirby M, Hirst C, and Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract.* 2011 Nov;65(11):1180-92.

Kulkarni et al 2016

Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med.* 2016 Oct;57(Suppl 3):97S-104S.

Kulkarni et al 2018

Kulkarni HR, Langbein T, Atay C, Singh A, Schuchardt C, Lehmann C, Pomper M, Pienta KJ, Baum RP. Safety and long-term efficacy of radioligand therapy using Lu-177 labeled PSMA ligands in metastatic prostate cancer: A single center experience over 5 years. *Cancer Research.* 2018 Jul;78(13): CT015.

Kratochwil et al 2015

Kratochwil C, Giesel FL, Eder M, Afshar-Oromieh A, Benešová M, Mier W, et al. [¹⁷⁷Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. *Eur J Nucl Med Mol Imaging.* 2015;42(6):987–88.

Kratochwil et al 2016

Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, Mier W, Eder M, Kopka K, Haberkorn U. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. *J Nucl Med.* 2016;57(8):1170-1176.

Leuschner 2016

Leuschner J. Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. LPT Report No. 32508 2016, November 12, 2016.

Loriot et al 2013

Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, ... and Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Annals of Oncology* 2013 24: 1807–1812. doi:10.1093/annonc/mdt136

Mannweiler et al 2009

Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, and Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. *Pathol Oncol Res.* 2009 June;15(2):167–72.

Noonan et al 2013

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Annals of Oncology* 2013;24: 1802–1807. doi:10.1093/annonc/mdt138

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001 Jul;33(5):337-43.

Rahbar et al 2016a

Rahbar K, Bode A, Weckesser M, Avramovic N, Claesener M, Stegger L, et al. Radioligand Therapy With 177Lu-PSMA-617 as A Novel Therapeutic Option in Patients With Metastatic Castration Resistant Prostate Cancer. *Clin Nucl Med.* 2016a;41(7):522-528.

Rahbar et al 2016b

Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. *J Nucl Med.* 2016b;57(9):1334-38.

Rahbar et al 2017

Rahbar K, Ahmadzadehfari J, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter Study Investigating 177Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients. *J Nucl Med.* 2017;58(1):85-90.

Rahbar et al 2018

Rahbar K, Boegemann M, Yordanova A, Eveslage M, Schäfers M, Essler M, Ahmadzadehfari H. PSMA targeted radioligand therapy in metastatic castration resistant prostate cancer after chemotherapy, abiraterone and/or enzalutamide. A retrospective analysis of overall survival. *Eur J Nucl Med Mol Imaging.* 2018 Jan;45(1):12-19.

Rajasekaran et al 2003

Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston WD, et al. A Novel Cytoplasmic Tail MXNN Motif Mediates the Internalization of Prostate-specific Membrane Antigen. *Mol Biol Cell.* 2003;14(12):4835-4845.

Rathke et al 2017

Rathke H, Giesel FL, Flechsig P, Kopka K, Mier W, Hohenfellner M, Haberkorn U, Kratochwil C. Repeated Lu-177-PSMA-617 radioligand therapy using treatment activities up to 9.3 GBq. *J Nucl Med.* 2017 Aug 10. pii: jnmed.117.194209. doi: 10.2967/jnmed.117.194209. [Epub ahead of print]

Rathore et al 2016

Rathore H, Shah H, Aland P, Chaudhuri P, Bharadwaj T, Kale C, et al. Assessment of response, clinical evaluation and toxicity of radioligand therapy (RLT) with 177-Lutetium-DKFZ-617-labelled Prostate specific membrane antigen (177-Lu-DKFZ-617-PSMA) for metastatic castrate

resistant prostate cancer (mCRPC): An initial experience in Jaslok. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S414 EP482.

Ross et al 2003

Ross JS, Sheehan CE, and Fisher H. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

Saad et al 2004

Saad F, Gleason DM, Murray R, Tchekmedyan S, Venner P, Lacombe L, et al. Long-Term Efficacy of Zoledronic Acid for the Prevention of Skeletal Complications in Patients with Metastatic Hormone-Refractory Prostate Cancer. J Natl Cancer Inst. 2004;96(11):879–82.

Scher et al 2015

Scher HI, Solo K, Valant J, Todd MB, and Mehra M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. PLoS One. 2015 Oct 13;10(10):e0139440.

Scher et al 2016

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Work Group 3. J Clin Oncol 2016;34(12):1402–18.

Siegel et al 2017

Siegel RL, Miller KD, and Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.

Smith et al 2016

Smith M, De Bono J, Sternberg C, Le Moulec S, Oudard S, De Giorgi U, et al. Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1. J Clin Oncol. 2016;34:3005-13.

Soydal et al 2016

Soydal C, Ozkan E, Nak D, and Kucuk ON. The First Experience on Lutetium (Lu)-177 Prostate Specific Antigen (PSMA) Treatment in Castration Resistant Prostate Cancer Patients. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S415 EP485.

Webster et al 2003

Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes. 2003 Dec 16;1:79.

Wegen et al 2016

Wegen S, Eppard E, Kürpig S, Essler M, Yordanova A, Hauser S, et al. Treatment response according to PSA changes in patients undergo more than one cycle of 177Lu-PSMA-617 therapy. Eur J Nucl Med Mol Imaging. 2016;43(Suppl 1):S213 EPW14.

Page 65 of 104

Weinfurt et al 2005

Weinfurt KP, Li Y, Castel LD, Saad F, Timbie JW, Glendenning GA, et al. The significance of skeletal-related events for the health related quality of life of patients with metastatic prostate cancer. Ann Oncol. 2005;16(4):579–84.

Yadav et al 2017

Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. ¹⁷⁷Lu-DKFZ-PSMA-617 therapy with metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91.

Yordanova et al 2017

Yordanova A, Becker A, Eppard E, et al. The impact of repeated cycles of radioligand therapy using [¹⁷⁷Lu]Lu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2017; DOI 10.1007/s00259-017-3681-9.

Zielinski et al 2014

Zielinski RR, Azad AA, Chi KN, Tyldesley S. Population-based impact on overall survival after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer. Can Urol Assoc J. 2014 Jul;8(7-8):E520-3.

Page 66 of 104

Appendix 1 Schedules of Assessments

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 July 2020

Table 3 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycle 1)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X-----				X-----	
AE monitoring ^a	X-----				X-----	
Weight	X ^b					
ECOG	X ^b					
Directed physical exam	X ^b					
Vital signs ^c	X ^b					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Administer ^{177}Lu -PSMA-617	X-----					
Best supportive/best standard of care	As per physician's orders					
Hematology ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Chemistry ^e	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Serum testosterone	X ^b					
PSA	X ^b					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)					

^a Adverse event monitoring will commence at time of consent.

^b Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (\pm 5) minutes before, 30 (\pm 5) minutes post, and 60 (\pm 5) minutes post ^{177}Lu -PSMA-617 administration.

^d To be completed prior to drug administration on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician or site research team member.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.
22 July 2020

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X ^c					X ^a	X ^a	X	
AE monitoring ^b	X					X ^a	X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{g,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Best supportive/best standard of care	As per physician's orders								
Hematology ^f	X ^c		X ^c		X ^c		X ^c	X	
Chemistry ^f	X ^c		X ^c		X ^c		X ^c	X	
Serum testosterone	X ^c						X ^c	X	
PSA	X ^c						X ^c	X	

Protocol no. PSMA-617-01
Version no. 4.4 DE

Endocyte, Inc.
22 July 2020

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 4 Schedule of assessments: ^{177}Lu -PSMA-617 plus best supportive/best standard of care arm (Cycles 2 to LTFU)

Study Period:	Cycles 2-6*						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			Collect:
Concomitant medication review	X ^c					X ^a	X ^a	X	<ul style="list-style-type: none"> • Hematology • Chemistry • Survival • New treatment: <ul style="list-style-type: none"> • Start/stop dates • Best response • Type of response • AE assessment • Radiographic imaging (only if pt came off the active part of the study for any reason other than radiographic disease progression)
AE monitoring ^b	X ^c					X ^a	X ^a	X	
Weight	X ^c						X ^c	X	
ECOG	X ^c						X ^c	X	
Directed physical exam	X ^c						X ^c	X	
Vital signs ^d	X ^c						X ^c	X	
EQ-5D-5L	X ^{e,h}						X ^{g,h}	X ^h	
FACT-P	X ^{e,h}						X ^{e,h}	X ^h	
BPI-SF	X ^{e,h}						X ^{e,h}	X ^h	
Administer ^{177}Lu -PSMA-617	X								
Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (± 4 days) after first dose of ^{177}Lu -PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks (± 4 days)								

* After the Cycle 4 dose of ^{177}Lu -PSMA-617 and prior to Cycle 5 Day 1, the investigator should determine if:

- The patient shows evidence of response (i.e. radiological, PSA, clinical benefit) and
- Has signs of residual disease on CT with contrast/MRI or bone scan and
- has shown good tolerance to the ^{177}Lu -PSMA-617 treatment.

If the patient meets the criteria above, and agrees to continue with additional treatment of ¹⁷⁷Lu-PSMA-617, the investigator may administer a further 2 cycles. A maximum of 6 cycles of radioligand therapy is allowed. If the patient does not meet all of the criteria or does not agree to additional ¹⁷⁷Lu-PSMA-617 treatment, then no additional doses of ¹⁷⁷Lu-PSMA-617 will be administered after Cycle 4. After the last cycle of ¹⁷⁷Lu-PSMA-617, patients can continue best supportive/best standard of care alone.

^{**} Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards. ^a Phone evaluation is allowed but are not required for visits after Day 1 of each cycle.

^b Adverse event monitoring will commence at time of consent.

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: within 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (within 3 days of Day 1) and at 15 (+/-5) minutes before, 30 (+/-5) minutes post, and 60 (+/-5) minutes post ¹⁷⁷Lu-PSMA-617 administration.

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done on Cycle 7 Day 1 and then every 12 weeks (\pm 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the last dose of ¹⁷⁷Lu-PSMA-617 or last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker or clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory - Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) - 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; WBC = white blood cell.

Table 5. Schedule of assessments: Best supportive/best standard of care only arm (Cycle 1) – (Not applicable for V4.4 DE)

Study Period:	Cycle 1					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cycle Week:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36
Concomitant medication review	X					X
AE monitoring ^b	X					X
Weight	X ^a					
ECOG	X ^a					
Directed physical exam	X ^a					
Vital signs ^c	X ^a					
EQ-5D-5L	X ^{d,f}					
FACT-P	X ^{d,f}					
BPI-SF	X ^{d,f}					
Best supportive/ best standard of care	As per physician's orders					
Hematology ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Chemistry ^e	X ^a	X ^a	X ^a	X ^a	X ^a	X ^a
Serum testosterone	X ^a					
PSA	X ^a					
Radiographic imaging (CT with contrast/MRI and bone scan)	Every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days) through the End of Treatment visit					

^a Can be done up to 3 days prior to Day 1. For hematology and chemistry: Up to 3 days prior to Days 1, 8, 15, 22, 29, and 36.

^b Adverse event monitoring will begin at time of consent.

^c Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^d To be completed prior to any drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^e Hematology and chemistry to be done every week for Cycle 1 only.

^f HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

^g Cycle 1 Day 1 for patients on the Best supportive/best standard of care only arm is considered as the day that the majority of the day 1 assessments are conducted.

AE = adverse event; BPI-SF Brief Pain Inventory – Short Form; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Protocol no. PSMA-617-01
Version no. 4.4 DE

Endocyte, Inc.
22 July 2020

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Table 6 Schedule of assessments: Best supportive/best standard of care only arm (Cycles 2 to LTFU) – (Not applicable for V4.4 DE)

Study Period:	Cycles 2-6**						After Cycle 6**	End of Treatment ^g	Long-term follow-up
Cycle Week:	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Every 12 weeks (± 4 days)		Every 3 months (± 1 month)
Cycle Day:	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36			
Concomitant medication review	X-----X ^a							X	
AE monitoring ^b	X-----X ^a							X	
Weight	X ^c						X ^b	X	
ECOG	X ^c						X ^b	X	
Directed physical exam	X ^c						X ^b	X	
Vital signs ^c	X ^c						X ^b	X	
EQ-5D-5L	X ^{e,h}						X ^{d,g}	X ^{d,g}	
FACT-P	X ^{e,h}						X ^{d,g}	X ^{d,g}	
BPI-SF	X ^{e,h}						X ^{d,g}	X	
Best supportive/best standard of care	As per physician's orders								
Hematology ^e	X ^c		X ^b		X ^b		X ^b	X	
Chemistry ^e	X ^c		X ^b		X ^b		X ^b	X	
Serum testosterone	X ^c						X ^b	X	
PSA	X ^c						X ^b	X	

Protocol no. PSMA-617-01
Version no. 4.4 DE

Endocyte, Inc.
22 July 2020

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Radiographic imaging (CT with contrast/MRI and bone scan)	To be conducted every 8 weeks (\pm 4 days) after first dose of best supportive/best standard of care for the first 24 weeks (independent of dose delays), then every 12 weeks (\pm 4 days)	
---	--	--

^{**}Cycles 2-6 are 6 weeks long. Cycle 7 Day 1 should occur after 6 full weeks from C6D1 (Day 43 of Cycle 6). Starting with Cycle 7, all cycles are 12 weeks long. The stipulated windows apply to C7D1 required procedures and for all cycles afterwards.

^a Phone evaluation are allowed but are not required for visits after Day 1 of each cycle. .

^b Adverse event monitoring will commence at time of consent.

^c Can be done up to 3 days prior to Day 1. For hematology and chemistry: up to 3 days prior to Days 1, 15, and 29.

^d Blood pressure, pulse and respiratory rate will be assessed at required physical exams (up to 3 days of Day 1).

^e To be completed prior to drug administration (if applicable) on Day 1. Can be completed up to 3 days prior to Day 1.

^f For Cycles 2 to 6: Hematology and chemistry to be done at Days 1, 15, and 29 (every 2 weeks). After Cycle 6, to be done every 12 weeks (\pm 4 days).

^g To be done once a patient is to enter the long-term follow-up part of the study. To occur approximately 30 days from the date of the last dose or intervention of best supportive/best standard of care end of treatment decision, but before the initiation of subsequent anticancer treatment, outside of what is allowed on study.

^h HRQoL and pain assessments may be self-completed by subject or administered in interview format and completed by a caretaker, clinician, or site research team member.

AE = adverse event; ANC = absolute neutrophil count; BPI-SF Brief Pain Inventory – Short Form; CBC = complete blood count; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EQ-5D-5L = European Quality of Life (EuroQoL) – 5-Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; WBC = white blood cell count

Appendix 2 Suggested treatment guidelines

The following are suggested guidelines for clinical support during ^{177}Lu -PSMA-617 administration. They are to be used at the discretion of the investigator.

- Cooling the salivary glands from 30 min. before and up to 4 hours after the ^{177}Lu -PSMA-617 injection for reducing the risk of salivary glands radiation injuries is optional and depends on center practice
- 500 mL of 0.9% (i.e., normal) saline may be infused at a rate of 125 mL/hour to begin after administration of ^{177}Lu -PSMA-617. Additionally, fluid intake should be encouraged on the day of treatment
- In patients with high tumor burden or gout allopurinol may be started within 7 days and up to 10 days following ^{177}Lu -PSMA-617 therapy

Appendix 3 Principal investigator signature

I have read this clinical protocol, no. PSMA-617-01, in its entirety and:

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal, and local laws and/or regulations
- I agree that this clinical protocol will not be modified by me or any member of my staff without the written consent of Endocyte, Inc. and, if required, I will receive approval of these modifications by my institution's IRB/REB/Independent Ethics Committee (IEC).
- I certify that neither I nor any member of my staff has been disqualified or debarred by the Food and Drug Administration (FDA), European or any other regulatory bodies for clinical investigations or any other purpose.
- I understand that this clinical protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless such disclosure is required by national, federal, or local laws and/or regulations.

Pursuant to 21 CFR § 312.53(c), each US investigator will complete and sign FDA Form 1572, Statement of Investigator, prior to participating in the study. The completed form, along with a curriculum vitae, will be returned to Endocyte and maintained on record.

Form FDA 1572, Statement of Investigator, which must be completed, is available at:
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Principal Investigator Signature

Date

Name (Printed)

Title (Printed)

Appendix 4a Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

Eastern Cooperative Oncology Group Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 4b Eastern Cooperative Oncology Group performance status scale and Karnofsky Performance Status comparison

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

*Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.

**Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramidate. *Journal of Chronic Diseases*; 1960;11:7-33.

Page 79 of 104

Appendix 5 Common Terminology Criteria for Adverse Events

The complete NCI CTCAE (version 5.0) can be found at the following site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Page 80 of 104

Appendix 6 Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:
<http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf>

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Appendix 7 Prostate Cancer Working Group 3 Recommendations

The sections that apply to this trial are the criteria for prostate-specific antigen (PSA) response and progression, and the criteria for bone lesion “prevent/delay end points” (progression). It is based on the PCWG3 recommendations. Please note that not all the recommendations listed below are applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	<ul style="list-style-type: none">Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drugMonitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progressionIgnore early rises (prior to 12 weeks) in determining PSA response <p>For control/relieve/eliminate endpoints:</p> <ul style="list-style-type: none">Describe absolute changes in PSA over time from baseline to best response <p>For delay/prevent endpoints: Decline from baseline:</p> <ul style="list-style-type: none">Record time from start of therapy to first PSA increase that is $\geq 25\%$ and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) <p>No decline from baseline:</p> <ul style="list-style-type: none">PSA progression $\geq 25\%$ and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	<p>For control/relieve/eliminate end points:</p> <p>Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats:</p> <ul style="list-style-type: none">Record up to 5 lesions per site of diseaseRecord changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separatelyOnly report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baselineRecord changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separatelyOnly report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimensionRecord complete elimination of disease at any site separatelyConfirm favorable change with second scanRecord changes using waterfall plot <p>For delay/prevent end points:</p> <ul style="list-style-type: none">Record changes in nodal and visceral disease separatelyRecord up to 5 lesions per site of spreadUse RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site. With additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies)Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1

Bone	<p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none"> Record outcome as new lesions, no new lesions or resolved lesion First scheduled reassessment: <ul style="list-style-type: none"> No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: <ul style="list-style-type: none"> No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: <ul style="list-style-type: none"> No new lesions: continue New lesions: progression Changes in intensity or uptake do not constitute regression or progression <p>For prevent/delay end points (progression):</p> <ul style="list-style-type: none"> Exclude pseudoprogression in the absence of symptoms or other signs of progression At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule) If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan Date of progression is the date of the scan that first documents the second lesion Changes in intensity of uptake alone do not constitute either progression or regression Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	<p>Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use).</p> <p>For control/relieve eliminate end points:</p> <ul style="list-style-type: none"> Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values <p>Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement.</p> <p>For delay/prevent end points:</p> <p>Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).</p> <p>Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).</p> <p>Time to deterioration of physical function and/or health-related quality of life (HRQoL) scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.</p>

Refer to [Scher et al 2016](#) for more details.

CNS = central nervous system; HRQoL = health-related quality of life; PCWG3 = Prostate Cancer Working Group 3; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors.

Page 83 of 104

Appendix 8 BPI-SF (*sample only, not for patient use*)

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Brief Pain Inventory (Short Form)

Time: _____ : _____ AM PM

Today's Date (day, month, year):
Day - JAN FEB MAR APR MAY JUN JUL AUG SEP OCT NOV DEC Year

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that best describes how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 1 of 2

Page 85 of 104

Today's Date (Day, Month, Year): <u> </u> - <u> </u> - <u> </u> (Example: 08-FEB-2016) <u> </u> DAY <u> </u> MONTH <u> </u> YEAR											
7. What treatments or medications are you receiving for your pain?											
8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.											
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Complete Relief
No Relief											
9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:											
A. General Activity											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
B. Mood											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
C. Walking Ability											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
D. Normal Work (includes both work outside the home and housework)											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
E. Relations with other people											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
F. Sleep											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
G. Enjoyment of life											
0	1	2	3	4	5	6	7	8	9	10	Completely Interferes
Does not Interfere											
Please place an "X" in the appropriate box to indicate who completed the form:											
<input type="checkbox"/> Patient											
<input type="checkbox"/> Another person read the patient the questions and marked the form with the patient's answers											

Copyright 1991 Charles S. Cleeland, PhD
Pain Research Group
All rights reserved

Page 2 of 2

Protocol no. PSMA-617-01
Version no.: 4.4 DE

Endocyte, Inc.

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Page 86 of 104

Appendix 9 EQ-5D-5L (European Quality of Life (EuroQol) – 5 Domain 5 Level scale) (sample only, not for patient use)

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Page 87 of 104



Health Questionnaire

English version for the UK

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

-
-
-
-
-

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

-
-
-
-
-

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

-
-
-
-
-

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

-
-
-
-
-

ANXIETY / DEPRESSION

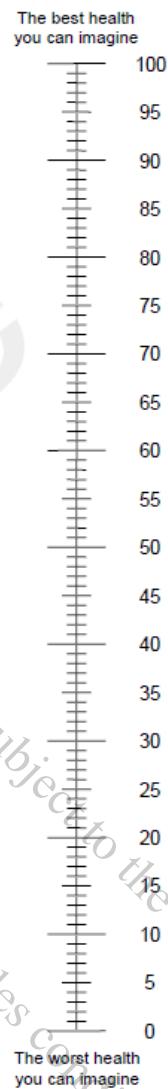
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

-
-
-
-
-

Page 89 of 104

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



3

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

Page 90 of 104

**Appendix 10 FACT-P (Functional Assessment of Cancer Therapy –
Prostate) (*sample only, not for patient use*)**

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

EMOTIONAL WELL-BEING

GE1
GE2
GE3
GE4
GE5
GE6

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness.....	0	1	2	3	4
I am losing hope in the fight against my illness.....	0	1	2	3	4
I feel nervous.....	0	1	2	3	4
I worry about dying.....	0	1	2	3	4
I worry that my condition will get worse.....	0	1	2	3	4

FUNCTIONAL WELL-BEING

GF1
GF2
GF3
GF4
GF5
GF6
GF7

	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (include work at home)	0	1	2	3	4
My work (include work at home) is fulfilling.....	0	1	2	3	4
I am able to enjoy life.....	0	1	2	3	4
I have accepted my illness.....	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun.....	0	1	2	3	4
I am content with the quality of my life right now.....	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNs	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight.....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
P1	I have aches and pains that bother me.....	0	1	2	3	4
P2	I have certain parts of my body where I experience pain....	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level.....	0	1	2	3	4
P5	I am able to feel like a man.....	0	1	2	3	4
P6	I have trouble moving my bowels.....	0	1	2	3	4
P7	I have difficulty urinating.....	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities.....	0	1	2	3	4
BL5	I am able to have and maintain an erection.....	0	1	2	3	4

Page 94 of 104

Appendix 11 PCCTC Bone Scan Assessment Tool

Protocol no. PSMA-617-01
Version no.: 4.4 DE

This information is confidential or privileged information and trade secrets of Endocyte, Inc.

Endocyte, Inc.

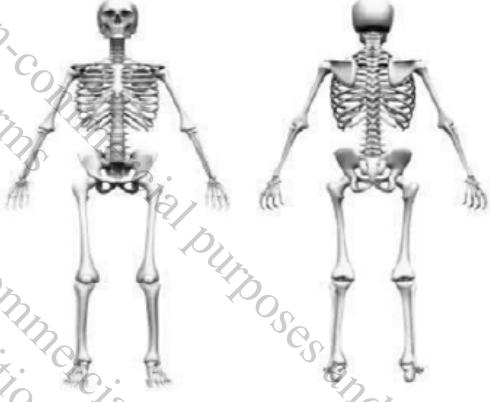
Page 95 of 104

Screening Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of lesions related to metastatic disease at Screening: <input type="checkbox"/> 1 <input type="checkbox"/> 2-4 <input type="checkbox"/> 5-9 <input type="checkbox"/> 10-20 <input type="checkbox"/> >20	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 96 of 104

Week 8 BASELINE Scan

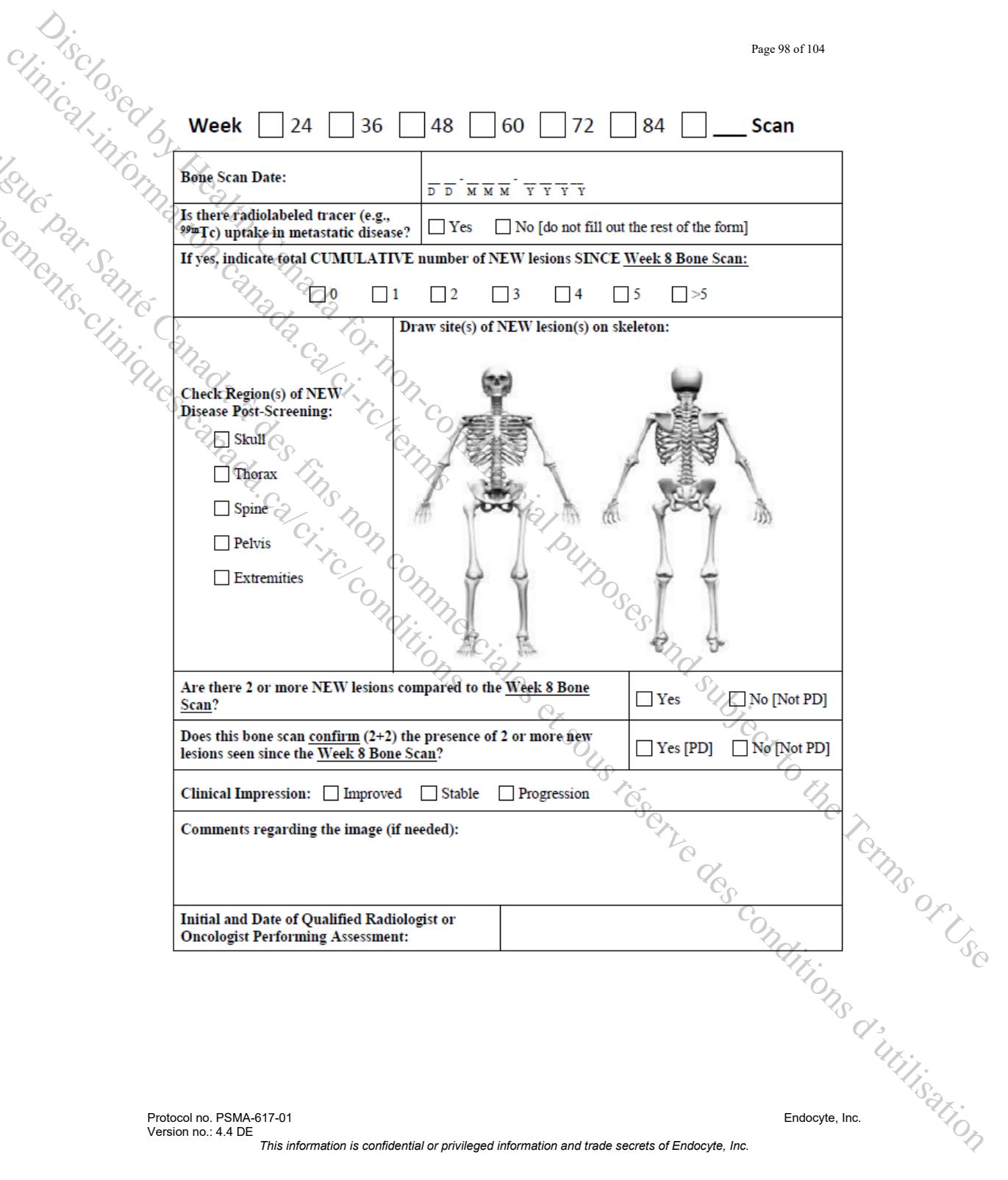
Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total number of NEW lesions compared to <u>Screening Bone Scan</u> :	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions at this <u>Week 8 Bone Scan</u> compared to the <u>Screening Bone Scan</u> ?	<input type="checkbox"/> Yes* <input type="checkbox"/> No
<i>* Presence of new lesions at this time does not confirm progression</i>	
Clinical Impression:	<input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Week 16 Scan

Bone Scan Date:	D D - M M M - Y Y Y Y
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan:	
<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening:	Draw site(s) of NEW lesion(s) on skeleton:
<input type="checkbox"/> Skull <input checked="" type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan?	
<input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Were there 2 or more NEW lesions at the Week 8 Bone Scan compared to the Screening Bone Scan AND were there 2 or more NEW lesions compared to the Week 8 Bone Scan?	
<input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

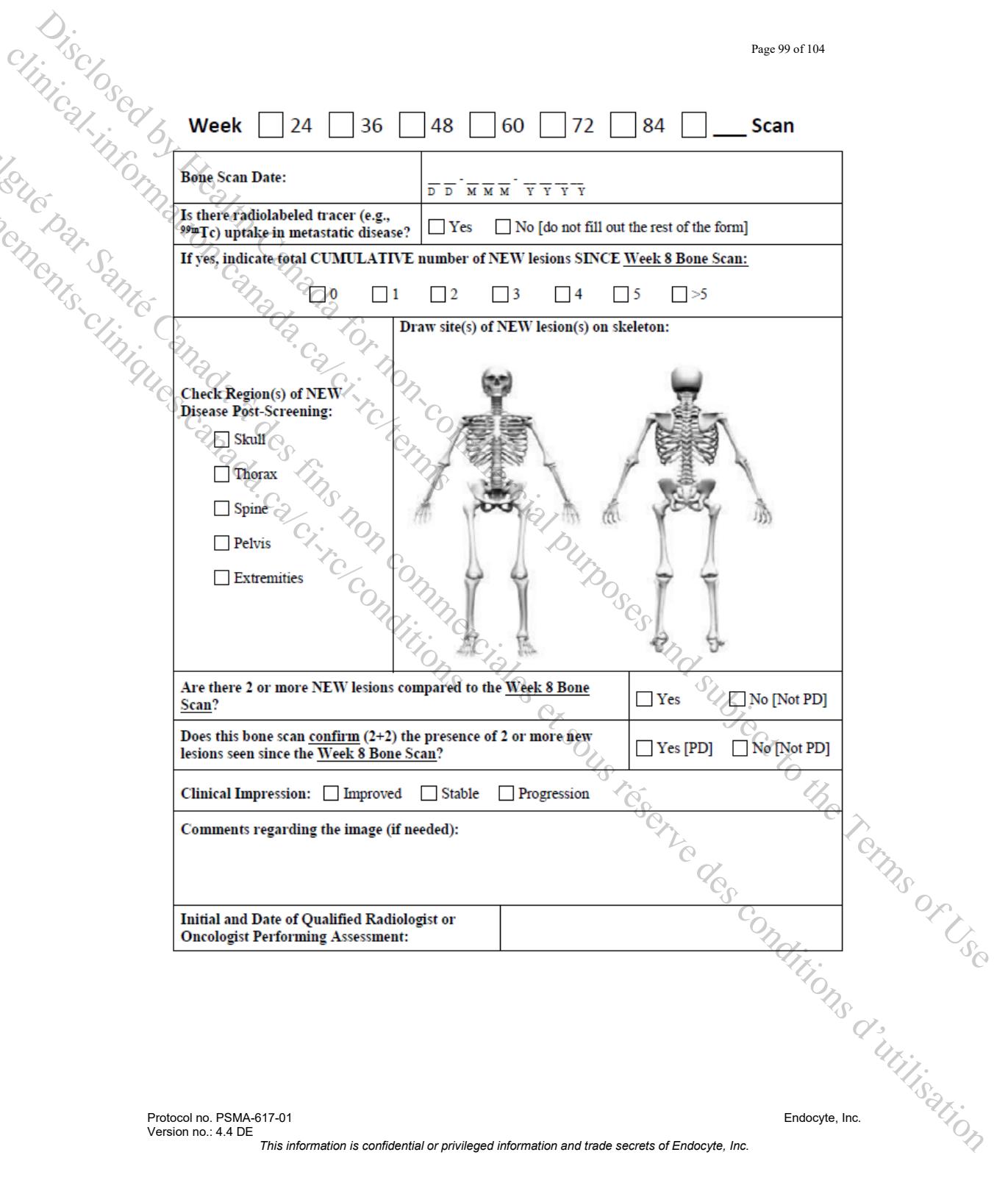
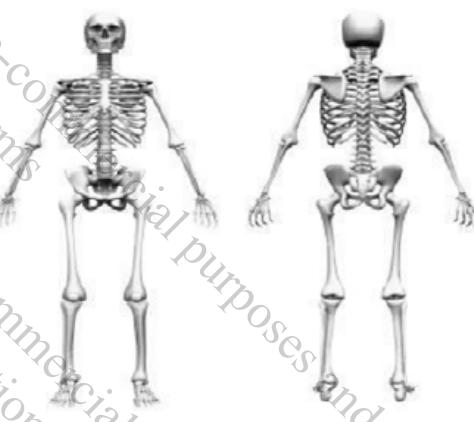
Page 98 of 104

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan <u>confirm</u> (2+) the presence of 2 or more new lesions seen since the <u>Week 8 Bone Scan</u> ? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

Page 99 of 104

Week 24 36 48 60 72 84 ___ Scan

Bone Scan Date: 	
Is there radiolabeled tracer (e.g., ^{99m}Tc) uptake in metastatic disease? <input type="checkbox"/> Yes <input type="checkbox"/> No [do not fill out the rest of the form]	
If yes, indicate total CUMULATIVE number of NEW lesions SINCE Week 8 Bone Scan: <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> >5	
Check Region(s) of NEW Disease Post-Screening: <input type="checkbox"/> Skull <input type="checkbox"/> Thorax <input type="checkbox"/> Spine <input type="checkbox"/> Pelvis <input type="checkbox"/> Extremities	Draw site(s) of NEW lesion(s) on skeleton: 
Are there 2 or more NEW lesions compared to the Week 8 Bone Scan? <input type="checkbox"/> Yes <input type="checkbox"/> No [Not PD]	
Does this bone scan confirm (2+) the presence of 2 or more new lesions seen since the Week 8 Bone Scan? <input type="checkbox"/> Yes [PD] <input type="checkbox"/> No [Not PD]	
Clinical Impression: <input type="checkbox"/> Improved <input type="checkbox"/> Stable <input type="checkbox"/> Progression	
Comments regarding the image (if needed):	
Initial and Date of Qualified Radiologist or Oncologist Performing Assessment:	

APPENDIX 12 DOSIMETRY, PK AND ECG SUB-STUDY

1. DOSIMETRY, PK AND ECG SUB-STUDY DESIGN

A dosimetry, PK and ECG sub-study will be conducted in a non-randomized cohort (¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617.

Data from the patients in the sub-study will not be considered in the primary and secondary analysis of the main study.

Patients participating in the sub-study will have been determined to be eligible for the main study and signed the informed consent specific to Germany.

Aside from the specific assessments conducted in the sub-study, as described below and the separate sub-study manual, the treatment regimen and patient care management will be identical to that implemented in the main study.

The results of this sub-study will be included in a Dosimetry Study Report addendum that will accompany the main study report.

2. AMENDMENT 4.4 RATIONALE

Due to local radioprotection laws and established guidelines in Germany, institutions are required to conduct additional imaging assessments following each given therapeutic dose of ¹⁷⁷Lu-PSMA-617 in order to investigate proper drug administration for patients participating in clinical trials. In an effort to align and comply with these local guidelines, additional assessments have been added to this sub-study protocol. These include imaging assessments and further surveillance for evaluating renal function.

3. OBJECTIVES

To evaluate dosimetry, pharmacokinetics, urine and ECG.

3.1 Primary Objective:

- Calculate whole body and organ radiation dosimetry of ¹⁷⁷Lu-PSMA-617 to further evaluate the dose to critical organs (e.g., kidney and bone marrow)

3.2 Secondary Objectives:

- Define the pharmacokinetic profile of ¹⁷⁷Lu-PSMA-617;
- Evaluate ECGs during treatment with ¹⁷⁷Lu-PSMA-617;

- Evaluate the safety and tolerability of ^{177}Lu -PSMA-617;
- Evaluate the metabolic stability of ^{177}Lu -PSMA-617

4. DOSIMETRY, PK AND ECG SUB-STUDY ASSESSMENTS

The sub-study patients will require whole body planar , 3D SPECT and CT imaging, urine collection, blood PK sampling and ECGs, at several time points during cycle 1 of treatment for complete dosimetry assessment, blood exposure, renal function, urinary metabolites and cardia assessments. Whole body planar and 3D SPECT localized to the abdomen will be performed from cycle 2 through cycle 6 of ^{177}Lu -PMSA-617 treatment.

Refer to Table 7 and the sub-study manual for timing assessments.

4.1 Imaging Assessments

Baseline images will be used to determine volumes in regions of interest in selected major source organs such as the liver, spleen and kidneys. Refer to the sub-study manual for further details on measurements and calculations.

4.1.1 Equipment

The following equipment will be required:

1. A gamma-camera with medium energy collimator.
2. A Co-57 flood source or a Lu-177 or Tc-99m filled flood source for the transmission scan. Well counter with multichannel analyzer or gamma counter to determine ^{177}Lu radioactivity in blood and urine samples.
3. A dose calibrator (activimeter) to measure the radioactivity in the reference source and the injected radioactivity.

4.2 PK Blood Sampling

Blood PK samples will be collected during cycle 1 of the treatment, to provide data for bone marrow radiation dose calculations and for PK assessment.

At cycle 1, blood samples (1mL) will be collected in heparinized tubes starting immediately before the start of administration, end of administration, then approximately 20mins (+/- 5mins), 60mins(+/- 5mins), 2hr (+/- 30mins), 4hr (+/- 30mins), 24hr (+/- 2hrs), 48hr (+/- 2hrs), 72hr (+/- 2hrs) & day 6 post end of infusion. Blood PK samples should be collected after ECGs, where timepoints overlap. Refer to Table 7 for the timing of assessments.

Radioactivity in blood will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time points have to be recorded by site. The exact time point of each measurement and the calibration factor must be documented by the investigational site.

4.3 Cardiac Assessments

A twelve-lead ECG test will be performed in triplicate for all patients during Cycle 1 of treatment for up to 4 time points (pre-administration and thereafter at approximately 1hr, 4hrs and 24hrs post treatment). Blood Pressure (BP) should be measured prior to each ECG time point.

In the event of a clinically significant finding (i.e., QTcF increase from baseline of >30ms occurs), an additional single safety ECG should be repeated prior to dosing at cycle 2.

All pre-medications will be administered during the time interval ranging from 90 mins to 60 mins before the start of infusion; the purpose of this requirement is to allow the recording of the baseline ECG intervals used in the primary ECG analysis and to capture the potential ECG effects of the pre-medication regimen.

If other treatments (other than pre-medications) are planned to be administered on Day 1, these should be administered at least 1hr before the start of infusion, as best as practically possible. In general, best effort will be made to avoid introducing new treatment between 1hr before, until 8hr after the start of infusion, unless clinically required.

Data obtained will be analyzed by a central reader to determine whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Clinically significant abnormalities will be recorded on the Adverse Event page of the eCRF.

ECG parameters will include HR, RR interval, PR interval, QRS interval and QT interval. QT intervals will be corrected for HR.

4.4 Urine

Total urine excreted will be collected between the end of infusion and the time of the first image (2hrs post infusion).

The extent of elimination of the radiolabeled compound must be determined before acquiring the first image. Therefore, the urine eliminated between the infusion and the time of the first image must be collected quantitatively (possibly in one single container), the whole volume or mass of this excreted urine must be measured and 1 mL sample withdrawn for radioactivity measurement. Radioactivity in urine will be measured at the investigational site, with a properly calibrated gamma counter or similar system. The exact time point of urine collection and measurement, as well as the calibration factor must be documented by the investigational site.

An aliquot (10 mL) of the whole urine collected between the infusion and the time of the first image will be also sent to a central laboratory for HPLC analysis. Moreover, for HPLC analysis purpose only, additional urine samples (around 10 mL, no need to have cumulative urine samples for this assessment) will be collected from the patients at 24hrs (+/-2hrs), 48hrs (+/-2hrs) and 72hrs (+/-2hrs). Collected samples will be sent to a central laboratory for analysis by HPLC according to a validated procedure, in order to determine the elimination of the radioactive compound and possible metabolites, if any, over time.

4.5 Renal Function Surveillance

In order to assess potential renal toxicity during the treatment phase of the study, the estimated glomerular filtration rate (eGFR) will be calculated from cycle 1 through cycle 6 with the most recent serum creatinine results collected using the Modification of Diet in Renal Disease (MDRD) equation. eGFR should be calculated prior to ^{177}Lu -PMSA-617 dosing in order to assess renal function.

Table 7 Sub-Study Assessment time points

Timepoint	Cycle 1 only						Cycle 2 through Cycle 6		
	eGFR calculation	Whole body planar imaging	3D SPECT/CT imaging	Blood sampling	BP & Intense ECG ^{b,d}	Urine	eGFR calculation	Whole body planar imaging	3D SPECT/CT imaging
Pre dose	X			X	X		X		
End of dose				X					
20 mins (+/- 5 mins)				X					
60 mins (+/- 5 mins)				X	X				
2 hours		X (1-2 hours) ^c	X (1-2 hours)+ CT	X (+/-30 mins)		X (end of dose to 2hrs) cumulative collection ^a			
4 hours (+/- 30 mins)				X	X				
24 hours		X ^c (18-26 hours)	X (18-26 hours)	X (+/-2 hr)	X (+/-2 hr)	X (+/-2 hr)			
48 hours		X (36-48 hours)	X (36-48 hours)	X (+/-2 hr)		X (+/-2 hr)	X (36-48 hr)	X (36-48 hr)	
72 hours				X (+/-2 hr)		X (+/-2 hr)			
Day 6				X					
156-168 hours		X	X						

^a Whole urine collection required between end of infusion and 2hrs post infusion, before the first image

^b Intense ECG monitoring required on day 1 cycle 1 only. Predose (Typically the patient lies supine at least 30 minutes prior to dosing. The triplicate ECGs are collected at approximately 1.5-2 min intervals during the last 5 minutes of the 30 minutes. The next triplicate is collected 1hr post dose, typically the patient is supine for 15 minutes (45 minutes post dose) and 3 readings are taken in last 5 minutes. The next triplicate is at 4hrs and the final at 24hrs and patient is supine resting for 15 minutes – after 10 minutes take 3 readings. ECG monitoring should be performed prior to blood collection.

^c After urine collection

^d BP to be collect prior to each ECG

Page 104 of 104

4.6 Measurements, Recording, Calculation and Analysis of Sub-study Data

Details regarding the methods used to measure, record and perform necessary calculations of the data acquired can be found in the sub-study manual.

**Pages 920 to 1081 were removed due to
being Out of Scope as per Health Canada's
Public Release of Clinical Information -
Imaging Manual.**

Divulgued by Health Canada for non-commercial purposes and subject to the Terms of Use
Divulgued by Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
renseignements-cliniques.canada.ca/ci-rc/terms
renseignements-cliniques.canada.ca/ci-rc/conditions

**Pages 1082 to 1190 were removed due to
being Out of Scope as per Health Canada's
Public Release of Clinical Information - Data
Monitoring Committee Charters.**

**Pages 1191 to 1428 were removed due to
being Out of Scope as per Health Canada's
Public Release of Clinical Information -
Imaging Review Charters.**

Divulgué par Santé Canada à des fins non commerciales et sous réserve des conditions d'utilisation
Renseignements-cliniques.ca/ri-rc/conditions
Divulgué par Santé Canada pour non-commercial purposes and subject to the Terms of Use
Renseignements-cliniques.ca/ri-rc/terms