

Appendix 16.1.9 Documentation of statistical methods

History of changes	
Version	Summary of changes
1.0	Original version

1 Statistical methods

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Statistical Analysis Plan
Addendum

Sponsor:

Protocol Title:

Endocyte, Inc.

VISION: AN INTERNATIONAL, PROSPECTIVE, OPEN-LABEL,
MULTICENTER, RANDOMIZED PHASE 3 STUDY OF¹⁷⁷LU-
PSMA-617 IN THE TREATMENT OF PATIENTS WITH
PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-
RESISTANT PROSTATE CANCER (mCRPC)

Protocol Number:

SAP Addendum Version, Version 1.0, 29 April 2021

Date:
(Addendum to SAP Version 3.0)

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1. LIST OF ABBREVIATIONS AND DEFINITION of TERMS

Abbreviation	Term/Definition
BPI-SF	Brief Pain Inventory – Short Form
CSR	Clinical study report
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
FACT-P	Functional Assessment of Cancer Therapy - Prostate
SAP	Statistical analysis plan

2. Introduction

This Statistical Analysis Plan (SAP) Addendum is to provide details on changes to the planned statistical analysis V3 for the primary clinical study report (CSR) under the protocol for clinical trial PSMA-617-01 (VISION).

2.1 Quality of Life (QoL) Analysis – BPI-SF

For QoL analyses, patient reported outcomes (PROs) were planned to be assessed using the questionnaires EQ-5D-5L, FACT-P, and BPI-SF. The definition for a threshold as needed for a subset of analyses for the BPI-SF needed to be updated since the definition as specified in SAP v3 did not account for patients with a zero scale at baseline for the respective scores. Namely the Pain Intensity and Pain Interference Scale thresholds as needed for time to event analyses are updated to be based on a threshold for worsening of ≥30% or ≥2-point increase of baseline instead of only ≥30% of baseline which is not possible to evaluate for patients with a zero scale (no pain) at baseline.

The change applies to the SAP section 8.2.3.3.3 table including description and scoring as displayed here with the change in terms of an addition to the "Threshold for worsening" for the Pain Intensity and Pain Interference Scale (marked in bold and underlined).

Description and Scoring (change marked in bold and underlined)

Scale Name	Number of Items	Scale Range	BPI-SF Item numbers	Threshold for worsening*
Individual Item Scales				
Worst pain intensity	1	0-10	3	Either of <u>≥30% of baseline</u> or <u>≥2-point increase**</u>
Least pain intensity	1	0-10	4	
Average pain intensity	1	0-10	5	
Pain intensity right now	1	0-10	6	
Summary Scales				
Pain Intensity Scale	4	0-10	3-6	<u>≥30% of baseline</u> or <u>≥2-point increase</u>
Pain Interference Scale	7	0-10	9a-9g	<u>≥30% of baseline</u> or <u>≥2-point increase</u>

*Minimally important difference for both 1) increase from baseline for within subject change and 2) between group differences for treatment comparisons.

**Analysis of worst pain intensity is included in Section 8.2.3.4 Health Economics Analysis as time to disease related pain (TDRP).

Aside from the change in threshold, the analysis definitions remain as in the SAP V3 and only the following analyses are affected by this change in threshold for worsening:

- Time to worsening of Pain Intensity Scale

- Time to worsening of Pain Interference Scale
- Time to improvement following initial pain worsening in Pain Intensity Scale
- Time to improvement following initial pain worsening in Pain Interference Scale

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PSMA-617 IN THE TREATMENT OF PATIENTS WITH
PROGRESSIVE PSMA-POSITIVE METASTATIC CASTRATION-
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1. LIST OF ABBREVIATIONS AND DEFINITION of TERMS

Abbreviation	Term/Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BOR	Best overall response
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSoC	Best standard of care
C1D1	Cycle 1 Day 1
CI	Confidence interval
CR	Complete response
CRO	Contract Research Organization
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDoR	Expected duration of response
EMA	European Medical Agency
EOT	End of Treatment
ESA	Erythropoietin stimulating agents
EuroQoL	European Quality of Life
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
EQ-VAS	European Quality of Life – Visual Analogue Scale
EWB	Emotional Well-Being
FACT-P	Functional Assessment of Cancer Therapy - Prostate
FACT-G	Functional Assessment of Cancer Therapy - General
FAPSI-8	Functional Assessment of Cancer Therapy Advance Prostate Symptom Index-8
FDA	Food and Drug Administration

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Abbreviation	Term/Definition
FAS	Full Analysis Set
FWB	Functional Well-Being
⁶⁸ Ga	Gallium-68
GM-CSF	Granulocyte macrophage colony-stimulating factor
HLGT	High level group terms
HLT	High level terms
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IRT	Interactive response technology
ITT	Intent to treat
LDH	Lactate dehydrogenase
LOS	Length of stay
¹⁷⁷ Lu	Lutetium-177
LTFU	Long term follow up
MAR	Missing at random
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NAAD	Novel androgen axis drug (such as abiraterone, enzalutamide, or apalutamide)
NCI	National Cancer Institute
NMQ	Novartis Medical Dictionary for Regulatory Activities (MedDRA) queries
OAU	Opioid analgesic use
ORR	Overall response rate
OS	Overall survival
PCS	Prostate Cancer Subscale
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PK	Pharmacokinetics
PET	Positron emission tomography
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PRS	Prostate Cancer Subscale Pain-Related Subscale
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
PT	Preferred term

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Abbreviation	Term/Definition
PWB	Physical Well-Being
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic progression-free survival
SAP	Statistical analysis plan
SD	Stable disease
SFWB	Social/Family Well-Being
SMQ	Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries
SOC	System organ class
SSE	Symptomatic Skeletal Event
TDRP	Time to disease-related pain
TEAE	Treatment-emergent adverse event
TFOA	Time to first use opioid analgesic
TOI	Trial Outcomes Index
TMF	Trial Master File
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization

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2. Introduction

This Statistical Analysis Plan (SAP) was written for the clinical trial PSMA-617-01 and is based on the current protocol version 4.0 dated 08 July 2019 and current country specific protocol version 4.4 DE dated 22 July 2020 that supports the sub-study conducted at sites in Germany. All decisions regarding the analyses, as defined in the SAP, have been made prior to database lock. The ICH guideline E3 "Structure and Content of Clinical Study Reports" was used as a guide to the writing of this SAP.

2.1 Changes from the Protocol

In protocol section 8.7.2, it states that the primary evaluation of the key secondary endpoints will be assessed in the PFS-FAS. While this is the case for the key secondary endpoint of time to first symptomatic skeletal event (SSE), the other key secondary endpoints, Overall Response Rate (ORR) and Disease Control Rate (DCR) per RECIST 1.1, will be assessed in the Response Evaluable Analysis Set defined as the subset of patients in the PFS-FAS with evaluable disease by RECIST 1.1 at baseline. In addition, the supportive analyses of ORR and DCR will not be performed in the FAS as the FAS would have included patients without RECIST evaluable disease and may result in bias due to the early dropout in the BSC/BSoC arm (see Section 3.1). Furthermore , the protocol specified that the time to first SSE will be analyzed using a Cox regression model, stratifying for the randomization factors however, the primary analysis of this endpoint will compare the treatment arms using the stratified log-rank test. The specific analyses that are planned for the key secondary endpoints are described in Section 8.2.2.

The analysis population PFS Analysis Set (PFS-FAS) as stated in protocol section 8.4, will be referred in the SAP and tables, listings and figures as PFS Full Analysis Set (PFS-FAS) as shown in Section 5.3.1.

As stated in section 8.3 of the protocol, the alpha level applicable to overall survival (OS) in the final analysis will depend upon the earlier radiographic progression-free survival (rPFS) and interim OS results. This implies that regardless of the interim analysis result of OS, final OS will be re-tested at the applicable alpha level. However, if the interim OS results are met at the pre-specified alpha level, the final OS will be presented descriptively without statistical inference and at the same nominal alpha level as specified in Section 3.4. In the event the formal interim OS analysis is not performed, the alpha level applicable to the final OS analysis will only depend on the final rPFS results. The details are further described in Section 4 and Section 8.2.1.

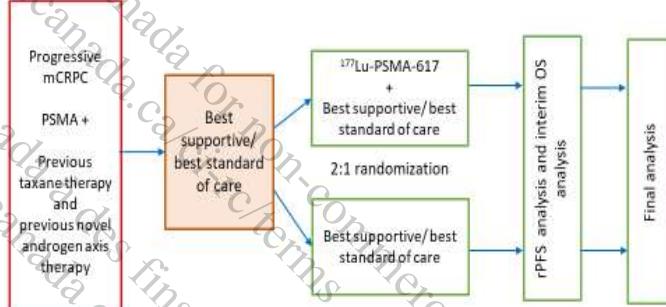
3. Study Design and Objectives

3.1 Study Design

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

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Figure 1 Diagram of trial design



Stratification Factors

- Serum lactate dehydrogenase [LDH] ($\leq 260 \text{ IU/L}$ vs. $> 260 \text{ IU/L}$)
- Presence of liver metastases (yes vs. no)
- ECOG score (0-1 vs. 2)
- Inclusion of NAAD in best supportive/best standard of care (yes vs. no)

Alternative Primary Endpoints

- Overall survival
- Radiographic progression-free survival (rPFS)

Key Secondary Endpoints [with α control]

- RECIST response
- Time to first symptomatic skeletal event (TSS)

Additional Secondary Endpoints

- Safety and tolerability
- Health-related quality of life (HQoL; EORTC QLQ-C30 and Brief Pain Inventory – Short Form (BPI-SF))
- Health economics
- Progression-free survival (PFS) (radiological, clinical or PSA progression)
- Biochemical response: PSA levels, alkaline phosphatase levels and lactate dehydrogenase levels

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

BSC/BSOC 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, abiraterone, or apalutamide) 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 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 BSC/BSOC (investigational arm) or to receive BSC/BSOC only (BSC/BSOC-only arm). Randomization will be stratified by 4 factors (Section 3.2).

Patients randomized to the investigational arm must begin ¹⁷⁷Lu-PSMA-617 dosing within 28 days of randomization. These patients will receive BSC/BSOC 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-617 and prior to Cycle 5 Day 1, the investigator should determine if:

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- The patient shows evidence of response (i.e. radiological, Prostate-specific antigen (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 BSC/BSoC alone.

BSC/BSoC 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 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, radiographic Progression-Free Survival (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. Crossover to ¹⁷⁷Lu-PSMA-617 treatment is not allowed.

An End of Treatment (EOT) visit should occur once a patient discontinues randomized 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 is 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 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, whichever is sooner.

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.

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 Overall Survival (OS), to be

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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 BSC/BSoC 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 5-Mar-2019. As part of the plan to address the early withdrawal of consent in the BSC/BSoC-only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 5-Mar-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 5-Mar-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.

Dosimetry, Pharmacokinetics and ECG Sub-study:

A dosimetry, pharmacokinetics (PK) and ECG sub-study will be conducted in a single arm, non-randomized cohort of approximately 30 patients at sites in Germany. These patients will receive the investigational treatment arm only (i.e., ¹⁷⁷Lu-PSMA-617 plus best supportive/best standard of care) and will provide a complete assessment of the safety aspects of ¹⁷⁷Lu-PSMA-617. To prevent biasing the results obtained from patients randomized in the main study, the patients enrolled in the sub-study will not be included in the analyses of the randomized main study but will be described separately from the main study. The data analysis of dosimetry, PK and ECG from the sub-study will be described in stand-alone analysis plan documents.

3.2 Randomization and Blinding

Eligible patients will be randomized by an interactive response technology (IRT) system in a 2:1 ratio to the investigational treatment arm or the BSC/BSoC -only arm using a permuted block scheme. The approximate 30 eligible patients included in the sub-study will not undergo randomization as all patients will receive the investigational treatment 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)

The study is open-label. However, access to subject treatment allocation will be limited to those individuals whose roles require access to perform their study responsibilities. Details of what roles and which individuals have access to unblinded data will be documented in a separate Data Access Plan maintained by the sponsor. Dates of access and reason for accesses will be recorded. Sponsor statisticians will be blinded and contract research organization (CRO) statisticians assigned to the study will be unblinded.

3.3 Study Objectives

Primary objective

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The primary objective of this study is to compare the two alternate endpoints of radiographic progression free survival (rPFS) per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines (Scher et al 2016) and overall survival (OS) in patients with progressive PSMA-positive mCRPC who receive ¹⁷⁷Lu-PSMA-617 in addition to BSC/BSoC versus patients treated by BSC/BSoC alone.

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 the first symptomatic skeletal event (SSE)

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)

3.4 Sample Size Justification

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 overall 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 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

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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.

4. Planned Analyses

The analyses of the alternate primary endpoints, rPFS and OS, are event driven. The formal planned analysis of rPFS is when 364 rPFS events have been observed in patients randomized on or after 5 March 2019 with an interim analysis of OS at the time of the rPFS analysis using all patients randomized since trial commencement (see Section 5.3.1 for Efficacy Populations). A final analysis of OS, using all patients randomized, will take place when 508 deaths have been observed.

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.

The alpha level applicable to OS in the final analysis will depend upon the earlier rPFS and interim OS results as described in Section 3.4. If the formal interim OS analysis is met at the pre-specified alpha level, the final OS will only be presented descriptively without statistical inference at the nominal alpha level. However, if the formal interim OS analysis is not performed, the alpha level applicable to the OS analysis will depend on the final rPFS results as follows:

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- if $p < 0.004$ 1-sided is achieved for rPFS, 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 not achieved for rPFS, then the alpha level for the final analysis of OS will be 0.021 1-sided.

4.1 Interim Analyses and IDMC Oversight

Safety data monitoring will be conducted quarterly by the Independent Data Monitoring Committee (IDMC). Safety reviews will commence following the completion of the first three months of study accrual. Safety analyses to be conducted are outlined in the IDMC charter. The specific responsibilities and composition of the IDMC are outlined in the IDMC Charter. The IDMC Charter will be approved and finalized by the IDMC members prior to the initiation of any formal efficacy analysis. 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 hypothesis testing will be conducted.

The planned analysis of rPFS and the interim analysis of OS will be overseen by the IDMC who may recommend stopping the study for superior efficacy at the first interim analysis for efficacy if the corresponding pre-specified 1-sided p-value threshold is met. The IDMC can recommend a course of action including early cessation if one of the alternate primary endpoints is met, 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.

4.2 Sub-study Analyses

The analyses of dosimetry, PK and ECG from the sub-study are described in separate analysis plans and are outside the scope of this SAP. All other analyses as described in this SAP will be performed, at the earliest, when all patients have completed study treatment (i.e. ^{177}Lu -PSMA-617+BSC/BSoC) or discontinued study treatment for any reason. Separate TFL shells will detail the planned outputs for the sub-study analyses.

5. General Analysis Definitions

Data will be analyzed using SAS version 9.4 or higher.

No tests of significance will be carried out to compare treatment arms on baseline data because any observed differences between them must be attributed to chance.

Descriptive statistics will be presented in tables as follows:

- Categorical data will be summarized in contingency tables presenting frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median, minimum, and maximum values.

Unless otherwise indicated, for frequency tables, patients with missing data will be excluded from the denominator of percentage calculations. All treatment arm comparisons other than the one-sided analyses described for the alternate primary endpoints, rPFS and OS, will be based on two-sided tests.

Tables will be created by treatment arm and for all patients combined as described at the beginning of sections 7, 8, and 9.

Individual patient listings will include all study-related data. The sort order of the listings will be by treatment, patient ID (center number-patient number), and date of assessment (if available).

Randomized treatment throughout this document will refer to ^{177}Lu -PSMA-617+BSC/BSoC and BSC/BSoC alone for analyses pertaining to the main study and will refer to ^{177}Lu -PSMA-617+BSC/BSoC for analyses pertaining to the sub-study.

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Best supportive/best standard of care (BSC/BSoC): BSC/BSoC in either arm will be administered as per physician's orders and protocol at the institution and whenever feasible, it should be optimized prior to randomization. Patients will continue to be treated with BSC/BSoC until they require a treatment regimen not allowed on study or have radiographic progressive disease as measured by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria. BSC/BSoC is defined as follows:

- Concomitant medications indicated as study BSC/BSoC, coded using WHO Drug Global dictionary. A pre-specified list of concomitant medications, based on the interventions allowed as BSC/BSoC per protocol (protocol section 5.2) will be used to indicate and flag concomitant medications as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will not be used to identify concomitant medications indicated as study BSC/BSoC.
- Concurrent procedures other than radiotherapy indicated as study BSC/BSoC, are coded using the Medical Dictionary for Regulatory Activities (MedDRA). The BSC/BSoC flag captured on the CRF will be used to identify concurrent procedures other than radiotherapy indicated as study BSC/BSoC.
- Concurrent radiotherapy indicated as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will be used to identify concurrent radiotherapy indicated as study BSC/BSoC.

Reference date is the date of first dose of randomized treatment unless otherwise noted.

Date of first dose of randomized treatment is defined as the date of first ¹⁷⁷Lu-PSMA-617 administration (non-zero dose) on Cycle 1 Day 1 (C1D1) or the date of first administration of BSC/BSoC.

- The date of first ¹⁷⁷Lu-PSMA-617 administration will be defined as the earliest date of administration as captured on the ¹⁷⁷Lu-PSMA-617 Administration CRF page with a non-zero dose.
- The date of first administration of BSC/BSoC will be defined as the date of C1D1.
- The date of first administration of a NAAD as study BSC/BSoC will be defined as follows:
 - = earliest start date of a NAAD indicated as study BSC/BSoC (captured on concomitant medications CRF) if after the date of first administration of BSC/BSoC, otherwise
 - = date of first administration of BSC/BSoC.

For example: if the earliest start date of a NAAD indicated as study BSC/BSoC is 01MAR2019 and the date of first administration of BSC/BSoC is 03JAN2019, then the date of first administration of a NAAD as study BSC/BSoC is 01MAR2019.

The number of days until a study assessment or procedure is calculated as:

- Study Day= Assessment date – Reference date +1 if assessment date is after or on the reference date
- Study Day= Assessment date – Reference date if assessment date is before the reference date

Note: The reference date for safety assessments during randomized treatment (e.g. adverse event onset, laboratory measurement, vital sign measurement, ECOG performance status, etc.) is the date of first dose of randomized treatment and the reference date for efficacy assessments (i.e. survival, tumor response, health related

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quality of life) is the date of randomization. The reference date for all assessments in the sub-study is the date of first dose of ^{177}Lu -PSMA-617.

Baseline for a given variable will be defined as the last non-missing assessment, including unscheduled assessments, for that variable obtained prior to or on the reference date but before the first treatment dose, unless otherwise noted.

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. For RECIST/PCWG3-based endpoints using CT/MRI, and bone scans (i.e. rPFS, ORR, DCR, duration of response, PFS), a window of 28 days from the start of randomized treatment will be allowed, i.e. the investigator/central review-reported responses will be maintained and baseline considered valid if the baseline assessment is within 28 days of randomized treatment start date. In the context of baseline definition, the efficacy evaluations also include the laboratory parameters PSA, ALP and LDH, and HRQoL (e.g. FACT-P). For safety evaluations of randomized treatment (i.e. laboratory assessments, ECOG performance status and vital signs), the last available assessment on or before the date of start of randomized treatment is taken as "baseline" assessment. For vital signs where time of assessment is captured (e.g. pre-dose and post-dose vital sign), the 15 minutes pre-dose value on or before the date of start of randomized treatment is taken as "baseline" assessment. For safety evaluations of ^{68}Ga -PSMA-11 (i.e. laboratory assessments and vital signs), the last available assessment on or before the date of ^{68}Ga -PSMA-11 is taken as "baseline" assessment.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If multiple values are from the same laboratory or collected for ECGs or vital signs, then the last value should be considered as baseline.

If patients have no value as defined, the baseline result will be considered as missing.

Refer to the table below for specific details on the baseline definitions for key study parameters.

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Parameter	Baseline Definition ¹	Evaluation
Baseline Height, Weight, Body Mass Index (BMI)	the last available assessment on or before the date of randomization	Baseline demographics and disease characteristics for randomized treatment
Baseline Height, Weight, Body Mass Index (BMI) prior to ⁶⁸ Ga-PSMA-11 dosing	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ⁶⁸ Ga-PSMA-11
Baseline ECOG score	ECOG score captured on the Enrollment CRF page Note: ECOG performance is not collected at the time of screening, therefore it will not be available for those not enrolled.	Baseline demographics and disease characteristics and Stratification Factor for randomized treatment
Baseline PSA, LDH and ALP	the last available assessment on or before the date of randomization	Baseline demographics and disease characteristics and Efficacy for randomized treatment
Baseline PSA,LDH and ALP prior to ⁶⁸ Ga-PSMA-11 dosing	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ⁶⁸ Ga-PSMA-11
Baseline lesions (per investigator and central review)	the last available assessment on or before the date of randomization and/or within 28 days of start of randomized treatment	Baseline disease characteristics and Efficacy for randomized treatment
Baseline lesions (per investigator) prior to ⁶⁸ Ga-PSMA-11 dosing	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Baseline demographics and disease characteristics for ⁶⁸ Ga-PSMA-11

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Baseline EQ-5D-5L, FACT-P and BPI-SF	the last available assessment on or before the date of randomization	Efficacy
Laboratory tests at baseline (chemistry, hematology, testosterone, urinalysis)	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
Laboratory tests at screening (chemistry, hematology, testosterone, urinalysis)	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Safety for ⁶⁸ Ga-PSMA-11
ECOG score at baseline	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
Vital signs at baseline	the last available assessment on or before the date of start of randomized treatment or if a time assessment is captured, the 15 minutes pre-dose value on or before the date of start of randomized treatment	Safety for randomized treatment
Vital signs at screening	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Safety for ⁶⁸ Ga-PSMA-11
ECG at baseline	the last available assessment on or before the date of start of randomized treatment	Safety for randomized treatment
ECG at screening	the last available assessment on or before the date of ⁶⁸ Ga-PSMA-11 dosing	Safety for ⁶⁸ Ga-PSMA-11

1. For the sub-study, randomized treatment refers only to ¹⁷⁷Lu-PSMA-617+BSC/BSoC.

Cycle 1 Day 1 (C1D1) is date of first study procedures, randomized treatment and assessments.

Date of randomization is used for the start date of "time to" endpoints for efficacy analyses.

⁶⁸Ga-PSMA-11 dosing is the date ⁶⁸Ga-PSMA-11 was administered.

Date of last randomized treatment administration is the date of last administration of randomized treatment which is the date of last administration of ¹⁷⁷Lu-PSMA-617 or date of last administration of BSC/BSoC, whichever is later. For example: if the last dose administration of ¹⁷⁷Lu-PSMA-617 is on 15APR2019, and the end of treatment decision

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date for BSC/BSoC is on 17APR2019, then the date of last administration of randomized treatment is on 17APR2019.

- Date of last administration of ^{177}Lu -PSMA-617 is the last date when ^{177}Lu -PSMA-617 was administered (non-zero dose), i.e. the latest date of administration as captured on the ^{177}Lu -PSMA-617 Administration CRF page with a non-zero dose.
- Date of last administration of BSC/BSoC is the end of treatment decision date recorded on the End of Treatment – BSC/BSoC CRF.
- Date of last administration of a NAAD as study BSC/BSoC will be defined as follows:
 - = latest end date of a NAAD indicated as study BSC/BSoC (captured on concomitant medications CRF) if before date of last administration of BSC/BSoC, otherwise
 - = date of last administration of BSC/BSoC.

For example: if the latest end date of a NAAD indicated as study BSC/BSoC is 01AUG2019 and the date of last administration of BSC/BSoC is 03OCT2019, then the date of last administration of a NAAD as study BSC/BSoC is 01AUG2019.

Last date of exposure to randomized treatment: The ^{177}Lu -PSMA-617 treatment schedule is organized in cycles of 42 days. The last date of exposure to randomized treatment is derived to be the latest date of the last date of exposure to either ^{177}Lu -PSMA-617 or BSC/BSoC. The last date of exposure to ^{177}Lu -PSMA-617 or BSC/BSoC will be derived as follows:

- The last date of exposure to ^{177}Lu -PSMA-617 is calculated as (last date of administration of ^{177}Lu -PSMA-617) + (length of time interval - 1) i.e. [last date of ^{177}Lu -PSMA-617 administration + (42-1)].
- If the subject died or was lost to follow-up (i.e. discontinued early from the study) within the last date of administration of ^{177}Lu -PSMA-617 + 42 days, the last date of exposure to ^{177}Lu -PSMA-617 is the date of death or date of last contact, respectively.
- The last date of exposure to BSC/BSoC is the last date of administration of BSC/BSoC (i.e. the end of treatment decision date recorded on the End of Treatment – BSC/BSoC CRF).
- The last date of exposure to a NAAD as study BSC/BSoC is the last date of administration of a NAAD as study BSC/BSoC.

Last contact date: The last contact date is derived for patients not known to have died at the analysis cut-off date based on the latest date among the following:

- Assessment dates (e.g. laboratory, vital signs, ECOG performance status/HRQoL (e.g. FACT-P), ECG, tumor imaging, end of treatment decision, etc.).
- Medication and procedure dates including ^{177}Lu -PSMA-617 administration, concomitant medications/therapies, concurrent surgical and therapeutic procedures (including radiation therapy), post-treatment cancer-related therapies after randomized treatment discontinuation (with non-missing medication/procedure term).
- Adverse event start and end dates (with non-missing verbatim AE term present).
- “Date of Last Contact” collected on the “Long Term Follow Contact” CRF.
- Randomized treatment start/end date
- Randomization date

The last contact date is defined as the latest complete date from the above list or the cut-off date, whichever comes first. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

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The last contact date is used for censoring of patients in the analysis of overall survival.

Time unit: A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

5.1 Study Periods and Visit Window Definitions

5.1.1 Study Periods

The study consists of 3 periods: screening, treatment (with no maximum number of cycles defined), and a follow-up period (end of treatment, long-term follow-up). Results will be presented by time point and not by period. However, the naming of the time points will reflect the period. In the investigational treatment arm, a patient will be treated with ¹⁷⁷Lu-PSMA-617 + BSC/BSoC up to a maximum of 6 cycles, and then BSC/BSoC only for the duration of the on-treatment period. Note that for cycles 1-6, cycle duration is 6 weeks, and for cycles 7 and beyond, cycle duration is 12 weeks.

5.1.2 Visit Windows

For data collected at multiple time points, the scheduled collection date/time will be used to summarize the data, unless otherwise indicated. Visits are scheduled from time of previous cycle's Day 1.

Scan assessments are scheduled from the reference date (date of first dose). Scan dates are not associated with a visit number. Dates are used for analyses and patient listings.

Unscheduled assessments will not be taken into account in summary variable calculations, except for baseline assessments and unscheduled RECIST, bone scan, PSA and HRQoL evaluations for evaluating efficacy (Section 8). All measurements will be presented in the listings.

Unless otherwise indicated, if more than one measurement (a lab result for example) exists for a patient on a particular time point/visit, the last value obtained at that time point/visit will be used when summarizing the data.

Refer to protocol section 6.1 and protocol Appendix 1 for schedules of study assessments during each study period.

5.2 Partial/Missing Dates

In general, the database requires a valid full date, including dates used for the alternate primary endpoints, rPFS and OS. However, for partial or missing dates for initial cancer diagnosis, prior therapies, and concomitant medication start dates, the rules shown below will be applied. (Concomitant medication stop dates and start and end dates for adverse events, concurrent radiotherapy, and concurrent surgical/therapeutic procedures are full date required fields.)

The imputed dates will only be used for the assignment to prior and/or concomitant medication or concurrent therapy and for deriving time since initial cancer diagnosis. The imputed dates will not be used in any other calculation and will not be listed.

For the calculation of the time since initial cancer diagnosis, the following imputation rules will be applied when the date of initial cancer diagnosis is incomplete:

- If the day is missing: first day of the month.
- If the day and month are missing: first day of January.

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For the assignment of medication, therapy and procedure to prior or concomitant/concurrent collected on the Concomitant Medication/Therapy, Concurrent Surgical / Therapeutic Procedures, and Radiotherapy CRF pages, the following rules will be applied for incomplete dates:

- If start date is incomplete:
 - if end date is before the date of first dose of randomized treatment, the start date will remain missing (i.e. prior);
 - if end date is on or after date of first study drug administration or the medication is ongoing,
 - if the day is missing: the start date will be imputed with the first day of the month;
 - if the day and month are missing: the start date will be imputed with 01 January of the year.

Note: Prior cancer related therapies, procedures and medications with missing or partial dates as captured on the Prior Cancer Related Surgery, Prior Radiotherapy and Prior Cancer Systemic Therapy CRF pages will not be imputed or included in the assignment of medications, procedures or therapies to prior or concomitant. Prior cancer related therapies will be summarized separately as described in Section 7.4.

The following rule should be used for the imputation of the date of last administration (end date) for BSC/BSoC:

- If the end date is completely missing and there is no End of Treatment (EOT) page and no death date/End of Study (EOS) date, the patient is considered as ongoing. The patient should be treated as on-going and the cut-off date should be used as the end date.

After imputation, compare the imputed date with start date of BSC/BSoC, if the imputed date is < start date of BSC/BSoC: Use the BSC/BSoC start date.

The following rules will be used for imputing adverse event (AE) start dates to assign as treatment emergent:

If day, month and year are missing:

- Completely missing start dates will not be imputed.

If day and month are missing:

- If partial start date year = year of randomized treatment start date then
 - If end date contains a full date and end date is earlier than randomized treatment start date then set start date = 01 January of the year
 - Else set start date = randomized treatment start date.
- If partial start date year > year of randomized treatment start date then 01 January of the year
- If partial start date year < year of randomized treatment start date then 01 July of the year

If day is missing:

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- If partial start date month and year = month and year of randomized treatment start date then
 - If end date contains a full date and end date is earlier than randomized treatment start date then set start date= first day of the month and year.
 - Else set start date = randomized treatment start date.
- If partial start date month and year > month and year of randomized treatment start date then first day of the month and year
- If partial start date month and year < month year of randomized treatment start date then 15th day of the month and year

Note: If randomized treatment start date is missing, apply the same rules but use the ⁶⁸Ga-PSMA-11 administration date instead.

For the assignment of an adverse event as a randomized treatment-emergent adverse event, the following rules will be applied when there is a partial date of subsequent anti-cancer treatment as captured on the post-treatment anti-cancer therapies or procedures CRF pages:

- if the day is missing: if the month of the partial subsequent anti-cancer treatment is in the same month as the date of last administration of randomized treatment (see Section 5), then impute using the date of last administration of randomized treatment. Otherwise, impute using the first day of the month.

5.3 Definition of Populations

5.3.1 Efficacy Populations

- **Full Analysis Set (FAS):** All randomized patients. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat analysis set. This analysis set will be used for the primary analysis of OS.
- **PFS Full Analysis Set (PFS-FAS):** All patients randomized on or after 5 March 2019. Patients will be included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set will be used for the primary analyses of rPFS and all secondary endpoints excluding ORR and DCR.
- **Response Evaluable Analysis Set:** The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment. See section 8.1 for details on how the final radiology assessment is selected.). Patients will be included in the treatment arm to which they were randomized. Soft tissue response as measured by RECIST will be assessed in this dataset. This analysis set will be used for the primary analyses of ORR and DCR.

5.3.2 Safety Populations

- **PSMA-11 Safety Analysis Set:** All patients who received a dose of ⁶⁸Ga-PSMA-11. This includes screened patients that are not enrolled (i.e., not randomized). Patients enrolled will be included in the treatment arm to which they were randomized.

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- **FAS Safety Analysis Set:** The subset of patients in the FAS who received at least one dose of randomized treatment. Patients will be included in the treatment arm corresponding to the actual treatment received.

5.3.3 Sub-study Populations

- **PSMA-11 Sub-study Analysis Set:** All patients who received a dose of ⁶⁸Ga-PSMA-11 in the sub-study conducted at sites in Germany. This includes screen failure patients who are not enrolled in the sub-study.
- **Sub-study Safety Analysis Set:** All patients who received at least one dose of the investigational treatment (¹⁷⁷Lu-PSMA-617+BSC/BSoC) in the sub-study conducted at sites in Germany.

5.4 Subgroup Definitions

The following subgroups are defined for the study:

1. Stratification Factor (based on CRF data) – Inclusion of NAADs (e.g., enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study (Yes vs. No). See Section 5.6 for derivation.
2. Number of cycles in the ¹⁷⁷Lu-PSMA-617 + BSC/BSoC treatment arm (≤ 4 cycles vs. 5–6 cycles).
3. Stratification factor (based on CRF data) – Baseline LDH (≤ 260 IU/L vs. > 260 IU/L). See Section 5.6 for derivation.
4. Stratification factor (based on CRF data) - Presence of liver metastases at baseline (Yes vs. No). See Section 5.6 for derivation.
5. Stratification factor (based on CRF data) – ECOG score at baseline (0 or 1 vs. 2). See section for derivation.
6. Age (< 65 years vs. ≥ 65 years)
7. Race (White vs. Black or African American vs. Asian vs. Other (includes "Native Hawaiian or Other Pacific Islander", "American Indian or Alaska Native" or more than one race reported)

5.4.1 Analyses on subgroups

All subgroup analyses are to be considered exploratory and descriptive; p-values presented with efficacy results will be treated as nominal.

Efficacy analyses The alternate primary endpoints, rPFS and OS, will be summarized and analyzed by the following subgroups (defined in Section 5.4) to assess the consistency of treatment effect provided either or both primary endpoints are statistically significant:

- Inclusion of NAADs as part of assigned BSC/BSoC treatment at start of study
- Baseline LDH
- Presence of liver metastases at baseline
- ECOG score at baseline
- Age
- Race

No formal statistical test of hypotheses will be performed for the subgroups. For each subgroup, a stratified cox regression model will be used to estimate the treatment effect

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stratifying for the randomization factors from IRT. When one of the stratification factors is the subgroup of interest, that factor will be excluded from the stratified model. The model will include three terms: treatment, subgroup (e.g. ECOG score at baseline) and treatment by subgroup interaction. The HR and associated confidence interval for each subgroup will be estimated from the model. Kaplan-Meier estimates as described for the alternate primary endpoints (Section 8.2.1) will also be provided excluding the log-rank test p-value. Subgroup analyses of rPFS and OS will be presented graphically using forest plots.

The efficacy analyses in subgroups will only be performed if at least 10% of patients or 10 patients are present in each class.

Key safety analyses of exposure, adverse events and clinical laboratory values will be performed as described in Section 9, on the FAS and PSMA-11 safety analysis sets (defined in Section 5.3.2) in the following subgroups (defined in Section 5.4):

- Inclusion of NAADs as part of assigned BSC/BSoC treatment at start of study (FAS Safety Analysis Set only)
- Number of cycles received in the ¹⁷⁷Lu-PSMA-617 + BSC/BSoC treatment arm (FAS Safety Analysis Set only)
- ECOG score at baseline (FAS Safety Analysis Set only)
- Age (FAS Safety Analysis Set and PSMA-11 Safety Analysis Set)
- Race (FAS Safety Analysis Set and PSMA-11 Safety Analysis Set)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of patients, or safety issues that are more commonly observed in a subgroup of patients. Summary tables will only be performed if at least 10% of patients or 10 patients are present in each subgroup.

The results of the efficacy and safety subgroup analyses will be presented in separate tables and figures from study arm results.

Separate listings will not be created for subgroups.

5.5 Treatment Arms

The following treatment arm labels will be used in the analysis:

- Lu-PSMA-617+BSC/BSoC: ¹⁷⁷Lu-PSMA-617 + Best supportive/best standard of care (investigational treatment arm)
- BSC/BSoC only: Best supportive/best standard of care only (control arm)

5.6 General Variable Definitions

- Time to withdrew consent from ¹⁷⁷Lu-PSMA-617 (days): (Date of withdrew of consent from ¹⁷⁷Lu-PSMA-617 treatment – date of randomization + 1).
- Time to withdrew consent from BSC/BSoC (days): (Date of withdrew of consent from BSC/BSoC – date of randomization + 1).
- Time to withdrew consent from study (days): (Date of withdrew of consent from study – date of randomization + 1).
- Age (years): year of informed consent - year of birth; calculated within clinical database.

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- Time since initial prostate cancer diagnosis (years): (Date of informed consent - Date of initial prostate cancer diagnosis)/(365.25). For incomplete dates, see Section 5.2.
- Weight (kg) = weight (lb) * 0.45359237
- Height (cm) = height (in) * 2.54
- BMI (kg/m^2) = weight[kg] / (height[m]²) using weight and height at baseline.
- Best % change (where a decrease over time is desirable) = ((smallest post baseline assessment – baseline)/baseline) x 100
- Last taxane therapy treatment-free interval (months): (randomization date - last taxane therapy end date)/(30.4375). For incomplete dates, see Section 5.2. Taxanes included are those identified as 'Taxane' per WHO Drug ATC Level 4 (e.g. cabazitaxel, docetaxel or paclitaxel).
- Baseline PSA doubling time (months): PSA doubling time will be calculated as natural log of 2 (0.693) divided by the sum of the fixed slope (common to all patients) and the random slope (specific for the patient) of the random coefficient linear model between the natural log of PSA and time of PSA measurement (Svatek et al., 2006). If the PSA doubling time is less than zero (i.e. stable, nonincreasing, or decreasing PSA levels as defined by a negative slope from the random coefficient linear model), the PSA doubling time is set to 0. PSA is collected at screening visit and for the most recent 2 PSA measurements available prior to screening. Calculations will be performed only for subjects with (1) all 3 PSA values with each value $\geq 0.2 \text{ ng/mL}$ and (2) for which the interval between the first and last PSA values are ≥ 8 weeks but ≤ 12 months as stated in PCWG3 guidelines (Scher et al., 2016; Pound et al., 1999).

For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy, and that 3 PSA values $\geq 0.2 \text{ ng/mL}$ should be consecutive. These additional criteria will not be applied since the information is not available.

- Randomized Treatment (i.e. ¹⁷⁷Lu-PSMA-617 and BSC/BSoC) Exposure Variables:

Average duration of randomized treatment cycles (months) = mean across cycles of (date of dosing for cycle n+1 – date of dosing for cycle n)/30.4375, where n=1 to total number of cycles minus 1.

Duration of exposure (months) = (Date of last exposure to randomized treatment – Reference date + 1)/30.4375. Date of first administration to randomized treatment and date of last exposure to randomized treatment are defined in Section 5.

For duration of exposure to ¹⁷⁷Lu-PSMA-617, the date of last exposure is the date of last exposure to ¹⁷⁷Lu-PSMA-617 and the reference date is the date of first administration of ¹⁷⁷Lu-PSMA-617.

For duration of exposure to BSC/BSoC, the date of last exposure is the date of last exposure to BSC/BSoC and the reference date is the date of first administration of BSC/BSoC (i.e. date of C1D1).

For duration of exposure to a NAAD as study BSC/BSoC, the date of last exposure is the date of last exposure to a NAAD as study BSC/BSoC and the reference date is the date of first administration of a NAAD as study BSC/BSoC.

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Dose intensity of ^{177}Lu -PSMA-617

Dose intensity overall (GBq/month) = (actual total dose of ^{177}Lu -PSMA-617 during the study) / (actual duration of the study (months)) Note: The duration of the last cycle will be set to 6 weeks (or ~ 1.37 months = 42 /30.4375).

Planned dose intensity overall (GBq/month) = (planned total dose of ^{177}Lu -PSMA-617 during the study) / (planned duration of the study (months))

Relative dose intensity overall (%) = (dose intensity overall) / (planned dose intensity overall)

Dose intensity of ^{177}Lu -PSMA-617 per cycle

Dose intensity per cycle (GBq/cycle) = (actual total dose of ^{177}Lu -PSMA-617 during the cycle)

Planned dose intensity per cycle (GBq/cycle) = (planned total dose of ^{177}Lu -PSMA-617 during the cycle)

Relative dose intensity per cycle (%) = (dose intensity per cycle) / (planned dose intensity per cycle)

Randomization Stratification Factors based on CRF data

Stratification factor (based on CRF data) - Baseline LDH (≤ 260 IU/L vs. > 260 IU/L) is defined as the latest LDH value on or before the date of randomization as collected on the laboratory CRF page.

Stratification factor (based on CRF data) - Presence of liver metastases at baseline (Yes vs. No) is defined as at least one target and/or non-target liver lesion on or before the date of randomization and/or within 28 days of start of randomized treatment as captured on either the target or non-target lesion CRF pages.

Stratification factor (based on CRF data) - ECOG score at baseline (0 or 1 vs. 2) is defined as the ECOG score captured on the Enrollment CRF page.

Stratification Factor (based on CRF data) – Inclusion of NAADs (e.g., enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study (Yes vs. No) is defined as having a NAAD indicated as study BSC/BSoC (see Section 5) on or before the date of C1D1.

6. Study Patients

6.1 Patient Disposition

Sample size flow will be displayed in a consort diagram, and the following patient data will be summarized in tables.

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Patient disposition for all patients who signed an informed consent:

- Number of patients who signed informed consent
 - Number of patients screened
 - Number of patients who were screen failures and the reason for screen failure
 - Number of patients administered ⁶⁸Ga-PSMA-11 (PSMA-11 Safety Analysis Set)
- By treatment arm and combined:
- Number of randomized patients – Full Analysis Set
 - Number of randomized patients on or after March 5, 2019 – PFS Analysis Set
 - Number (%) of patients in Response Evaluable Analysis Set
 - Number of randomized patients administered study treatment (FAS Safety Analysis Set)

Enrollment by country and center will be summarized for all screened patients and also by treatment arm using the FAS.

End of treatment status and the end of study status for all patients in the FAS, PFS-FAS and in the FAS randomized prior to 5 March 2019 will be summarized, by treatment arm and combined:

- Number (%) of patients treated, not treated and still on treatment
- Number (%) of patients discontinued from ¹⁷⁷Lu-PSMA-617 and BSC/BSoC, separately and all study treatments
- Number (%) for each primary reason for discontinuation from ¹⁷⁷Lu-PSMA-617 and BSC/BSoC, separately
 - Number (%) for reason for withdrawal of consent for ¹⁷⁷Lu-PSMA-617 and BSC/BSoC, separately
 - Time to withdrew consent (in days) continuous and categorical (1,2-28, 29-56, >56)
- Number (%) of patients continuing in long-term follow-up period (i.e. patients who agreed to long-term follow-up and have not discontinued from the study)
- Number (%) of patients discontinued from study
- Number (%) for each primary reason for discontinuation from study
 - Number (%) for reason for withdrawal of consent for ¹⁷⁷Lu-PSMA-617 and BSC/BSoC, separately
 - Time to withdrew consent (in days) continuous and categorical (1, 2-28, 29-56, >56)

6.1.1 Sub-study

Patient disposition for all patients who signed an informed consent in the sub-study will be summarized and will include the following: Number of patients who signed informed consent, Number of patients screened, Number of patients who were screen failures and the reason for screen failure, Number of patients administered ⁶⁸Ga-PSMA-11 (PSMA-11 Sub-study Analysis Set), Number of patients administered ¹⁷⁷Lu-PSMA-617 and BSC/BSoC (Sub-study Safety Analysis Set). End of treatment and end of study status will also be summarized as described above for all patients in the Sub-study Safety Analysis Set.

6.2 Protocol Deviations

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For the FAS, major protocol deviations will be summarized for each treatment arm and overall. The details of all deviations (major and minor) will also be listed by treatment and patient ID. All Protocol deviations (major and minor) will be recorded as part of the Trial Master File (TMF).

Specific protocol deviation categories will be assigned to important deviations related to COVID-19 (e.g. missing efficacy assessments and treatment interruptions) and these will be summarized separately and flagged in the listings.

6.2.1 Sub-study

A listing of all deviations (major and minor) will be listed for the Sub-study Safety Analysis Set. Specific protocol deviations related to COVID-19 will be flagged in the listing.

6.3 Inclusion and Exclusion Criteria

For all screened patients, a summary of all inclusion criteria not met and exclusion criteria met will be provided. An additional summary will be provided for the PSMA-11 Safety Analysis Set. A listing, including the protocol version the patient was consented under and a flag for the FAS population, will be provided for all screened patients.

6.3.1 Sub-study

A listing of all inclusion criteria not met and exclusion criteria met will be provided for all screened patients in the sub-study.

6.4 Stratification Information

For the FAS, PFS-FAS and the Response Evaluable Analysis Set, the number (%) of patients in each randomization stratum based on data obtained from the IRT system and data collected on the CRF (see Section 5.6) will be summarized by treatment arm and overall. The randomization stratification factors are: LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care (yes vs no) at time of randomization. Discordance between the stratum recorded in the IRT system and the actual stratum through data collected in the CRF will be cross-tabulated for the FAS, PFS-FAS and Response Evaluable Analysis Set and listed for the FAS.

7. Baseline Characteristics and Prior and Concurrent Therapies and Medications

All tables in Section 7 will be presented by treatment arm and for all patients combined for the FAS, PFS-FAS, the Response Evaluable Analysis Set, FAS Safety Analysis Set and the PSMA-11 Safety Analysis Set (defined in Section 5.3) unless otherwise specified. For tables using the PSMA-11 Safety Analysis Set, an additional column will be included for patients not enrolled (i.e. not randomized).

7.1 Demographic and baseline assessments

Descriptive statistics of patient characteristics at baseline will be presented for the following:

- Age (years): continuous and categorical (<65 vs. ≥ 65 , <65 vs. $\geq 65-84$ vs. ≥ 85)
- Race (White vs. Black or African American vs. Asian vs. Others (includes "Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native")

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- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- ECOG performance status (0 or 1 vs. 2) Note: ECOG performance status is captured on the Enrollment CRF page and not collected at the time of screening. Thus, ECOG performance status will not be available for those not enrolled.

7.2 Baseline Disease Characteristics

Descriptive statistics of patient disease characteristics at baseline will be presented for the following variables:

- Time since initial prostate cancer diagnosis (years)
- Initial Histopathological Classification
- Initial Histopathological Grade
- Initial Gleason score
 - Categorical: 2-3, 4-7, 8-10, unknown
- Stage at Initial Diagnosis
- Total Sum of Target Lesions Diameters per RECIST 1.1
- Baseline Target Lesions (Yes vs. No) and Non-Target Lesions (Yes vs. No)
- Site of disease (lung (yes/no), liver (yes/no), lymph node (yes/no), bone (yes/no), other (yes/no) using target and non-target lesions or bone scan assessments (bone only); sponsor to provide categorization)
- Baseline PSA doubling time (months): continuous and categorical (≤ 6 vs. >6)
- Baseline PSA
- Baseline ALP
- Baseline LDH

Note: The baseline variables 'Total Sum of Target Lesions Diameters', 'Target Lesions and Non-Target Lesions' will be based on the data collected on target/non-target lesion assessment according to RECIST 1.1 according to local investigator assessment and documented in the CRF. 'Site of disease' will be based on the data collected on either the target/non-target lesion assessment (per RECIST 1.1) or the bone scan assessment per local investigator assessment and documented in the CRF.

7.3 Medical History

Relevant medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

The relevant medical conditions will be tabulated separately for active (ongoing) and not-active conditions by system organ class (SOC) and preferred term (PT). Medical history events will be marked as ongoing if still active at time of informed consent.

7.4 Prior Cancer Related Therapy

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Descriptive statistics with respect to prior therapy will be displayed. A listing of all data recorded on the Prior Cancer Related Surgery, Prior Radiotherapy and Prior Cancer Systemic Therapy CRF pages will also be provided.

Prior cancer related surgery will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and prior cancer systemic therapy will be coded using the WHO Drug Global dictionary. The MedDRA and WHO Drug Global dictionary versions used for reporting will be specified as a footnote in the applicable tables and listings.

The variables to be summarized in tables are:

- Prior Prostate Cancer-related Surgery
 - Number of patients with at least one prostate cancer-related Surgery (including biopsies)
 - Prior number of prostate cancer-related surgeries/biopsies
 - Reason for prior surgery (Therapeutic, Diagnostic/Biopsy, Palliative, Other)
- Prior Prostate Cancer-related Radiotherapy
 - Number of patients with at least one Prostate Cancer-related Radiotherapy
 - Prior number of radiotherapies
 - Unique Sites
- Prior Prostate Cancer-related Systemic Therapy: All Therapies
 - Prior number of NAAD-containing regimens
 - Prior number of taxane-containing regimens
 - Reason for therapy
 - Number of unique agents
 - Type of prior therapy (by ATC Level 4 and WHO Drug preferred name). Type of prior therapy will be presented by ATC level alphabetically and preferred name is sorted within ATC class alphabetically.
- Prior Prostate Cancer-related Systemic Therapy: Last Taxane Therapy
 - Last taxane therapy is defined as the last taxane as part of a taxane-containing regimen, prior to study entry.
 - Reason for Therapy
 - Number of cycles
 - Duration of therapy (months): (last taxane therapy stop date - last taxane therapy start date + 1)/30.4375. Incomplete dates will not be imputed.
 - Progression
 - PSA progression (yes, no, not applicable, unknown)
 - Bone progression (yes, no, not applicable, unknown)
 - Soft tissue progression (yes, no, not applicable, unknown)
 - Type(s) of progression (New lesions, existing lesions, new and existing lesions, not applicable, unknown)
 - Treatment-free interval (months, defined in Section 5.6)
 - Best overall response (BOR) to last taxane-therapy (Complete response (CR), Partial response (PR), Stable disease (SD), Progressive Disease (PD), Not Available, Unknown)
 - Duration of historic BOR (CR or PR) (months): (date of progression (earliest of PSA, bone or soft tissue) - date of best response (CR or PR) + 1)/30.4375. Incomplete dates will not be imputed.
 - Reason last taxane therapy ended

7.5 Sub-study

Baseline demographics and baseline disease characteristics will be summarized for the Sub-study Safety Analysis Set and will be summarized and listed for PSMA-11 sub-study analysis set. Medical history and prior cancer therapy will be listed for the PSMA-11 Sub-study Analysis Set.

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8. Efficacy Evaluation

8.1 Efficacy Variable Definitions

In general, time to event and duration endpoints (e.g. rPFS), in number of days, is calculated as:

Days = event/censor date – reference date (e.g. randomization date) +1. If a patient has no assessment after first dose, censoring is at date of randomization. See Section 5 for converting time units.

Radiographic imaging will be assessed locally by each site and entered into the CRF. Additionally, patient scans will be collected for independent central review and data will be enter into the imagining CRF at the vendor. The independent central review will be used for the primary analyses of radiographic progression-free survival per PCWG3, overall response rate, disease control rate and duration of response using RECIST 1.1 and progression-free survival. The final radiology assessment as determined by the independent reviewer and described in the imagining review charter will be used for the analysis of these endpoints. At the time of analysis and prior to database lock, the two independent radiologists (radiologist 1 and radiologist 2) will each perform a global read and make a final determination of rPFS for the patient. If there is a difference in patient level determination of progressive disease (PD) between the two independent radiologists, a third radiologist will adjudicate the final assessment. The adjudicator will select which of the two independent radiologists' reads (radiologist 1 or radiologist 2) he/she agrees with more for RECIST/PCWG3 PD determination. The selected radiology read (i.e. radiologist 1 or radiologist 2) by the adjudicator will be the final radiology assessment for the patient. If there is no adjudication, the final radiology assessment defaults to radiologist 1. Refer to Imaging Review Charter for more details.

The local radiographic imaging assessment will be used for patient management at the site and will be compared to central assessments to evaluate concordance as described in the IDMC charter and mock tables. The local investigator assessment as captured on the CRF will be used as a sensitivity analysis for radiographic progression-free survival only.

8.1.1 Primary Efficacy Definitions

Overall Survival (OS) (months): (Date of death/censor - Date of randomization + 1)/30.4375. OS is defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient is not known to have died, then OS will be censored. The censoring date is date of last contact (see Section 5), i.e. the date the patient was last known to be alive.

Radiographic progression-free survival (rPFS) (months): (Date of radiographic PD/death/censor – date of randomization + 1) / 30.4375. rPFS is defined as the time (in months) from the date of randomization to the date of radiographic disease progression as outlined in PCWG3 Guidelines (Scher et al 2016; protocol Appendix 7, RECIST v1.1; FDA guidance, 2007; EMA guideline, 2012) or death due to any cause.

- o Note:

- In the investigational treatment arm, a patient continues to be in the treatment period of the study on BSC/BSoC after receiving their final dose of ^{177}Lu -PSMA-617.

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- Patients are at risk of the different types of rPFS events for different lengths of time:
 - RECIST v1.1 (Soft tissue) PD can occur up through last scan, which can be during long term follow-up (LTFU).
 - Bone PD can occur up to scan prior to last scan (with confirmation at last scan), which can be during LTFU.
 - Death can occur up through 24 weeks past the last study scan, or if no post treatment scans, up to 24 weeks after the first randomized treatment dose (based on the 2 missed visits censoring rule)
- Date of radiographic progressive disease (radiographic PD) event: date of the first CT/MRI/bone scan PD/death due to any cause occurs with no more than 1 immediately prior missing assessment.
 - RECIST 1.1 PD
 - Assessment in which Overall RECIST v1.1 Response is PD
 - Date of PD is date of first appearance of the new lesion(s), if applicable.
 - Bone scan PD must be confirmed as follows (rules allow for a flare effect at the first post-treatment scan). See examples in Appendix B:
 - Rule 1 (Progression at week 8 confirmed at week 16): If there are at least two new lesions on the first post-treatment scan, they must be confirmed with at least two additional lesions on the next scan (2+2 rule). The date of progression is the date of the first post-treatment scan.
 - Rule 2 (Progression at week 16 or later confirmed at next scan): For scans after the first post-treatment scan, there must be at least two new lesions relative to the first post-treatment scan (treating as a new baseline) that remain persistent (confirmed) on a subsequent scan. The date of progression is the date of the scan that first documents the second lesion compared to first post-treatment scan.
- Date of Censoring for rPFS:
 - The censoring date is the date when the last evaluable radiographic assessment (CT/MRI/bone scan) determined a lack of progression.
 - If there were no evaluable assessments, censoring occurs at the date of randomization.
 - Patients who have 2 or more consecutive missed tumor assessments immediately prior to progressive disease (PD) or death will be censored at the date of the last evaluable tumor assessment prior to those missing tumor assessments. Study scans are every 8 weeks +/- 4 days for the first 24 weeks, then every 12 weeks +/- 4 days and are scheduled relative to date of first dose of randomized treatment. Thus, subjects are considered as having 2 missed assessments if:
 - day 117 ≤ study day of event scan ≤ day 229 and time since last evaluable assessment ≥ 118 days
(2 missed visits, 117 = 16 weeks + 4 days + 1; 229 = 24 weeks + 8 weeks + 4 days + 1)
 - day 230 ≤ study day of event scan ≤ day 313 and time since last evaluable assessment ≥ 146 days

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(2 missed visits, 145 = 20 weeks + 4 days + 1; 313 = 24 weeks + 20 weeks + 4 days + 1)

- study day of event scan \geq day 314 and time since last evaluable assessment \geq 174 days

(2 missed visits, 173 = 24 weeks + 4 days + 1)

8.1.2 Key Secondary Efficacy Definitions

- RECIST responses for patients with measurable disease at baseline (RECIST guidelines v1.1, Eisenhauer et al., 2009)
 - Overall Response Rate (ORR) = Proportion of patients with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR). ORR is based on RECIST v1.1 response for patients with measurable disease at baseline.

Patients with no evaluable RECIST evaluations after baseline will be considered non-responders.

Soft tissue CR or PR needs to be confirmed at the next scan that is evaluable at least 4 weeks later. The following rules will be taken into account to define the BOR:

- CR = at least two determinations of CR at least 4 weeks or later
- PR = at least two determinations of PR or better (i.e. CR) at least 4 weeks or later apart (and not qualifying for CR)
- SD = at least one Stable Disease (SD) assessment or better (i.e. CR or PR) $>$ 6 weeks after first dose of randomized treatment (and not qualifying for CR or PR)
- Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) $>$ 6 weeks after first dose of randomized treatment (and not qualifying for CR or PD).
- PD = Progressive Disease (PD) at first evaluable scan after first dose of randomized treatment (and not qualifying for CR, PR or SD)
- Disease Control Rate (DCR) = Proportion of patients with BOR of CR, PR, SD, or Non-CR/Non-PD according to RECIST v1.1.
 - Same rules for no post baseline evaluations and for confirmation of CR and PR
 - Also, best response of SD or Non-CR/No-PD must be at least 6 weeks after date of first dose.

Duration of response (DOR) (months) (only for patients with a tumor response of CR or PR): (Date of RECIST PD/death/censor – Date of Best Overall Response + 1)/30.4375.) DOR is defined as the duration between the date of first documented best overall response and the date of first documented radiographic progression or death due to any cause. Date of Best Overall Response is the date of the first RECIST response of CR or PR of the confirmed response endpoint Overall Response Rate. Censoring rules are the same as for rPFS, except using only soft tissue scan dates (excluding bone scan dates).

- Time to first symptomatic skeletal event (SSE, months): (Date of SSE/censor – Date of randomization + 1)/30.4375. Time to first SSE is defined as the time (in months) from the date of randomization to the date of the SSE or death from any cause. SSE date is 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 due to any cause, whichever occurs first. SSE

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data for this endpoint is collected up through EOT visit.

Censoring date is date of the last study visit (on or before EOT visit).

8.1.3 Additional Secondary Efficacy Definitions

- **Progression-free survival (PFS) (months):** (Date of first radiographic progression/clinical progression/PSA progression/death/censor – Date of randomization + 1)/30.4375. PFS is defined as the time (in months) from the date of randomization to the date of first evidence of radiographic, clinical or PSA progression or death due to any cause, whichever occurs first. The dates of radiographic, clinical and PSA progression are defined as follows:
 - **Date of radiographic progression:** defined in Section 8.1.1.
 - **Date of clinical progression:** earliest date of assessment for when the investigator indicates clinical progression has occurred.
 - **Date of PSA progression:** Where a decline from baseline is documented, date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir (from all scheduled and unscheduled visits prior to the current visit being evaluated) is documented and confirmed by a second value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks of date of first dose of randomized treatment will be ignored.
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 from the date of first dose of randomized treatment (with confirmation obtained 3 or more weeks later) as specified in PCWG3 guidelines.
 - **Date of censoring for PFS:** Censoring date is the same as defined for rPFS.
- **PSA doubling time (months):** PSA doubling time will be calculated as natural log of 2 (0.693) divided by the sum of the fixed slope (common to all patients) and the random slope (specific for the patient) of the random coefficient linear model between the natural log of PSA and time of PSA measurement (Svatek et al., 2006). If the PSA doubling time is less than zero (i.e. stable, nonincreasing, or decreasing PSA levels as defined by a negative slope from the random coefficient linear model), the PSA doubling time is set to zero. The calculation will be based on (1) latest baseline PSA measurement ≥ 0.2 ng/mL, (2) at least three consecutive (scheduled and unscheduled) post-baseline PSA values with each value ≥ 0.2 ng/mL, and (3) interval between first and last PSA values of ≥8 weeks but ≤ 12 months as stated in PCWG3 guidelines (Scher et al., 2016; Pound et al., 1999).

If the baseline PSA value prior to first dose of randomized treatment is missing or < 0.2 ng/mL, PSA doubling time will be missing.

For interpretation of PSA doubling time it should be noted that PCWG3 guidelines state the calculation should be based on the most recent PSA values during androgen deprivation therapy. These additional criteria will not be applied.

- **PSA response:** PSA response is defined as the proportion of patients who have a ≥50% decrease in PSA from baseline that is confirmed by a second PSA measurement ≥4 weeks later. All scheduled and unscheduled PSA assessments will be used to determine and confirm PSA response.
- **PSA > 80% decrease:** PSA ≥ 80% decrease is defined as the proportion of subjects that have a ≥80% decrease in PSA from baseline that is confirmed by a second PSA

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measurement ≥ 4 weeks later. All scheduled and unscheduled PSA assessments will be used to determine and confirm a PSA $\geq 80\%$ decrease.

- Duration of PSA response (only for patients with response) (months): (date of PSA progression/censor – Date of PSA response + 1)/30.4375. Duration of PSA response is defined as the duration (in months) between the date of first document PSA response (i.e. $\geq 50\%$ decrease in PSA from baseline) and earliest date of PSA progression as defined above. The censoring date is the date of last PSA assessment.

8.1.4 Sub-study

For all efficacy variable derivations, the date of first dose of ^{177}Lu -PSMA-617+BSC/BSoC, as defined in Section 5, will be used as the reference date instead of the date of randomization. All efficacy derivations will be based on local investigator assessment; no central assessments will be performed.

8.2 Efficacy Analyses

The primary analysis of rPFS per independent central review will be based on the PFS-FAS while the primary analysis of OS will be based on the FAS. The analyses of the secondary efficacy endpoints will be performed on the PFS-FAS, defined in Section 5.3, except for soft tissue response (ORR and DCR) as measured by RECIST 1.1, for which the primary analysis will be performed on the Response Evaluable Efficacy Analysis Set. The randomization stratification factors from the IRT system will be used for all efficacy analyses unless otherwise specified.

All data summaries will be presented by treatment arm.

8.2.1 Primary Efficacy Analyses

The alternate primary efficacy endpoints are OS and rPFS (defined in Section 8.1.1). For the primary analysis of rPFS with an interim analysis of OS, and final analysis of OS (see Section 4), the analyses described below will be done using 1-sided tests of treatment differences. If the formal interim OS analysis is met at the pre-specified alpha level, the final OS will only be presented descriptively without statistical inference at the nominal alpha level specified in Section 3.4. However, if the interim analysis of OS is not performed, the alpha level applicable to the OS analysis will depend on the final rPFS results as described in Section 4.

Overall Survival

The null hypothesis for OS, as stated in Section 3.4, will be tested at a one-sided level of significance. The primary analysis is to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization-stratification factors. The alternate primary efficacy variable, OS, will be analyzed at the interim analysis and final analysis as defined in Section 4.

The primary analysis of OS at the interim and final analysis will be based on the FAS population. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.8% confidence intervals at the interim analysis and 95% or 96% confidence intervals at the final analysis (depending on the earlier rPFS and interim OS results, Section 3.4 or depending on the final rPFS results if the interim OS analysis is not performed, Section 4) will be presented for each treatment arm. The OS Kaplan-Meier estimate along with 99.8% confidence intervals at the interim analysis and 95% or 96% confidence intervals at the final analysis, will be presented at different time points (e.g. 6, 12, and 18 months) for each treatment arm. The one-sided p-value from the log-rank test will be presented at the interim and final analysis.

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A supportive analysis will be performed in terms of a stratified Cox regression model with a single covariate for randomized treatment arm, stratifying again for the randomization stratification factors. The hazard ratio for OS will be calculated, along with its 99.8% confidence interval at the interim analysis and its 95% or 96% confidence interval at the final analysis, from the stratified Cox model. The HR and CI from this model will be used as an adjunct to the primary stratified log-rank test p-value to provide the quantification of the treatment effect on OS.

The following data will be provided for the analysis of OS:

- Median follow-up (months) with 95% CI using the Kaplan-Meier method, censoring for deaths, and range
- Kaplan-Meier curves with 99.8% confidence limits at interim and 95% or 96% confidence limits at final and number at risk
- Number (%) events and censored, reason censored (alive, lost to follow-up, withdrew consent)
- Kaplan-Meier median, 25th percentile, and 75th percentile with 99.8% CIs at interim and 95% or 96% CIs at final
- Overall Survival rates and standard errors at 6 months, 12 months, and 18 months with 99.8% CIs at interim and 95% or 96% CIs at final
- Cox regression HR (active: control) with 99.8% CI at interim and 95% or 96% CI at final
- Log-rank test 1-sided p-value

Visual checks of the proportional hazard assumption will be performed based on the Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS. No formal analysis will be generated. If the proportional hazard assumption doesn't hold, additional methods may be explored to assess the treatment effect. Further details will be provided in a separate post-hoc analysis plan.

Radiographic Progression-Free Survival

The null hypothesis for rPFS per independent central review, as stated in Section 3.4, will be tested at a one-sided level of significance. The primary analysis is to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The alternate primary efficacy variable, rPFS, will be analyzed when 364 rPFS events have occurred (Section 4).

The primary analysis of rPFS will be based on the PFS-FAS population. The rPFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.2% confidence intervals will be presented for each treatment arm. The rPFS Kaplan-Meier estimate along with 99.2% confidence intervals will be presented at different time points (e.g. 3, 6, and 12 months) for each treatment arm. The one-sided p-value from the log-rank test will be presented.

A supportive analysis will be performed in terms of a stratified Cox regression model with a single covariate for randomized treatment arm, stratifying again for the randomization stratification factors. The hazard ratio for rPFS will be calculated, along with its 99.2% confidence interval, from the stratified Cox model. The HR and CI from this model 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.

The following data will be provided for the analysis of rPFS:

- Median follow-up (months) with 95% CI using the Kaplan-Meier method, censoring for radiographic progressions or deaths, and range
- Kaplan-Meier curves with 99.2% confidence limits and number at risk

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- Number (%) events and censored, reason censored (ongoing without event, event documented after 2 or more missed tumor assessments, adequate assessment not available)
- Kaplan-Meier median, 25th percentile, and 75th percentile with 99.2% CIs
- rPFS rates and standard errors at 3 months, 6 months, and 12 months with 99.2% CIs
- Cox regression HR (active: control) with 99.2% CI
- Log-rank test 1-sided p-value

Visual checks of the proportional hazard assumption will be performed based on the Plots (SURVIVAL LOGSURV LOGLOGS) generated by LIFETEST procedure in SAS. No formal analysis will be generated. If the proportional hazard assumption doesn't hold, additional methods may be explored to assess the treatment effect. Further details will be provided in a separate post-hoc analysis plan.

Sensitivity and supportive analyses for rPFS:

For all sensitivity and supportive analyses of the alternate primary endpoints, rPFS and OS, the nominal one-sided p-value will be provided without any statistical inference.

First Sensitivity analysis of rPFS: This sensitivity analysis is the same as the primary rPFS analysis (Section 8.1.1) except with additional rPFS events as follows:

- Includes events regardless of intervening missed assessments.
- Bone PDs are indicated by one of the following per PCWG3 guidelines:
 - Rule 1 (Progression at week 8 and confirmed at week 16): same as Rule 1 described in Section 8.1.1.
 - Modified Rule 2 (Progression at week 16 or later without confirmation): PD can still only occur at the second post treatment scan or later. The date of bone PD is the date when there are at least two new lesions relative to the first post-treatment scan without confirmation.
- Includes all radiographic PD and deaths captured in the study, including scans not centrally read that are captured on the LTFU CRF page.

This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Second Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except with additional censoring as follows:

- Deaths occurring after start of a new anti-cancer therapy will be censored at start date of new therapy.

This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Third Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except rPFS will be defined from the date of first dose of randomized treatment. This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Fourth Sensitivity analysis: This sensitivity analysis is the same as the primary rPFS analysis except using local investigator assessments. This sensitivity analysis will use the PFS-FAS population and will compare the two treatment arms using the same analysis conventions described in Section 8.2.1.

Sensitivity analyses to assess the impact of COVID-19:

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The impact of missing PCWG3 (bone scans) and/or RECIST assessments on the primary rPFS analysis caused by COVID-19 will be evaluated by the existing first sensitivity analysis.

The following analyses of rPFS will be used to estimate the treatment effect in the absence of the COVID-19 virus:

- Analysis as per the primary rPFS analysis but censoring COVID-19 related deaths at the last adequate assessment prior to the death.
- An analysis as per the 'first sensitivity analysis' but censoring COVID-19 related deaths at the date of death.

For the analyses above, the patients with COVID-19 related deaths will be determined in a blinded fashion by clinical review of the data and will be documented prior to database lock.

The same analyses conventions used for the primary analyses of rPFS, as described in section 8.2.1, will be performed (without p-values).

Supportive analyses of rPFS:

rPFS will be derived in all patients randomized (FAS population) using the same conventions as described in Section 8.1.1 but will consider patients randomized before March 5, 2019 who withdrew consent from the study (i.e. no further data on radiographic progression is available) as (1) censored at time of withdrawal and (2) a rPFS event at the time of withdrawal.

The following data will be summarized using the FAS:

- (1): Number (%) rPFS events (radiographic PD, deaths) and censored, reason censored (ongoing without event, withdrew consent, event documented with two or more missed tumor assessments, adequate assessment not available)
- (2): Number (%) rPFS events (radiographic PD, deaths, withdrew consent) and censored, reason censored (ongoing without event, withdrew consent, event documented with two or more missed tumor assessments, adequate assessment not available)

Missing tumor assessments: The number of patients with at least one missing/not evaluable tumor assessment (TA) based on independent central review will be presented together with the following breakdown categories: number of patients with 1, 2, 3, 4, 5, >5 missing/not evaluable TAs. The purpose of this analysis is to gain an insight as to whether the TAs have been carried out in accordance with the protocol and to understand if any meaningful discrepancies exist between the pattern of missing assessments by treatment arms. Timing of all tumor assessments will be depicted graphically and displayed by treatment arm.

Since the planned tumor assessments are every 8 weeks in the first 24 weeks from C1D1 and every 12 weeks thereafter, the following time windows (in weeks) will be constructed for each patient from the date of randomization: (note the open parenthesis such as (12, 20] indicates that week 12 doesn't belong to this interval and week 12+1 day belongs to that interval)

- Until ~24 weeks post randomization [0, 12], (12, 20], (20, 28]
- After ~24 weeks post randomization (28, 42], (42, 54], (54, 66], ...

where '0' is the patient's date of randomization. Every time-window (with the exception of the initial, broader one) is centered at the scheduled time of a TA, i.e., around week 16, week 24 for second and third window respectively, etc. A patient will be considered 'at risk' of missing a TA for any one of these time-windows if the patient either:

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- is 'on study' for at least the first 4 weeks of the time-window for the first 24 weeks (8 weeks for the first time window), or at least the first 6 weeks of time-window thereafter, i.e., if the patient is ongoing at the time of the scheduled TA, or
- discontinued treatment due to documented disease progression within the specific time window.

For example, if a patient discontinued due to documented disease progression during Week 24, then the patient would have been 'at risk' of a missing/not evaluable TA for the [20, 28] week time window.

For the purpose of this analysis, 'not evaluable' TAs (i.e., evaluations with an overall tumor response of 'not evaluable' per central independent review) will be considered to be missing. However, a clear distinction between 'truly missing' and 'present but not evaluable' needs to be made in the derived dataset to allow for both a combined analysis, i.e. missing and not evaluable treated the same, and separate analyses.

TAs performed after a documented radiographic disease progression per independent central review will not be considered. In other words, the final time-window for which a patient would be at risk of a missing/not evaluable scan would be that during which the documented radiographic progression occurred.

For patients without documented radiographic progression per independent central review, all TAs are considered up to the earliest of the following dates: death, the analysis cut-off, discontinuation due to disease progression, withdrawal of consent or loss to follow-up.

Concordance between local and central review: A summary on censoring reasons will be produced for rPFS by investigator and central radiology. The censoring patterns will be compared between investigator and central review. A comparison of rPFS event type/censor between local radiology review and central radiology review will be provided using the PFS-FAS population.

Sensitivity and supplementary analyses for OS:

Supplementary analysis of OS:

A supplementary descriptive analysis of OS will be performed using the PFS-FAS population. This analysis will use the same analysis conventions described in Section 8.2.1 but will be descriptive with the nominal p-value presented.

Sensitivity analyses to assess the impact of COVID-19:

The following analyses of OS will be used to estimate the treatment effect in the absence of the COVID-19 virus:

- Analysis as per the primary OS analysis but censoring COVID-19 related deaths at the date of death.

For the analyses above, the patients with COVID-19 related deaths will be determined in a blinded fashion by clinical review of the data and will be documented prior to database lock.

The same analyses conventions used for the primary analyses of OS, as described in section 8.2.1, will be performed (without p-values).

Subgroup analyses for rPFS and OS:

If either of the primary efficacy analyses of the alternate endpoints are statistically significant, the alternate primary endpoints of rPFS and/or OS will be summarized for subgroups, as specified in Section 5.4.1. Subgroup analyses of rPFS and OS will be presented graphically using forest plots.

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8.2.2 Key Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. To control the overall Type I error rate, if either alternate primary endpoint is met (see Section 4), 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 key secondary endpoints.

The alpha level applicable to the analysis of the key secondary endpoints will depend on the statistically significant results of the final rPFS or the statistically significant results of OS at either the interim or final analysis as follows:

Analysis of Key Secondary Endpoints at Interim and Final OS Analysis

Scenario	Final rPFS/Interim OS Analysis			Final OS Analysis	
	Final rPFS 1-sided p-value	Interim OS 1-sided p-value	2-sided alpha (CI) for Key Secondary Endpoints	Final OS 1-sided p-value	2-sided alpha (CI) for Key Secondary Endpoints
A	p<0.004	p<0.001	0.01 (99%)	Not re-tested ¹	Not re-tested ²
B	p<0.004	NS	Not tested ³	p<0.024	0.048 (95.2%)
				NS	Not tested ⁴
C	NS	p<0.001	0.002 (99.8%)	Not re-tested ¹	Not re-tested ²
D	NS	NS	Not tested ³	p<0.02	0.040 (96%)

NS: Not statistically significant at pre-specified alpha level.

CI: Confidence interval

1. Final OS will not be re-tested if the interim OS is met. The final OS results will be presented descriptively including 95% CI and the nominal p-value.
2. The key secondary endpoints will not be re-tested if the final OS is met however, the results will be presented descriptively including 95% CI and the nominal p-value.
3. The key secondary endpoints will not be tested if interim OS is not met however, the results will be presented descriptively including 95% CI and the nominal p-value.
4. If the key secondary endpoints are tested when final OS is not met using the successful rPFS 1-sided (2-sided) alpha level of 0.004 (0.008), there will be, at most, a type I error inflation of 0.004 because the rPFS alpha level has already been allocated to the final OS test. Therefore, if final OS is not met, the key secondary endpoints will only be presented descriptively including 95% CI and the nominal p-value.

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Analysis of Key Secondary Endpoints at Final rPFS/Final OS Analysis

Scenario	Final rPFS/Final OS Analysis		
	Final rPFS 1-sided p-value	Final OS 1-sided p-value	2-sided alpha (CI) for Key Secondary Endpoints
A	p<0.004	p<0.025	0.05 (95%)
B	p<0.004	NS	Not tested ¹
C	NS	p<0.021	0.042 (95.8%)
D	NS	NS	Not tested ²

NS: Not statistically significant at pre-specified alpha level.

CI: Confidence interval

1. If the key secondary endpoints are tested when final OS is not met using the successful rPFS 1-sided (2-sided) alpha level of 0.004 (0.008), there will be, at most, a type I error inflation of 0.004 because the rPFS alpha level has already been allocated to the final OS test. Therefore, if final OS is not met, the key secondary endpoints will only be presented descriptively including 95% CI and the nominal p-value.
2. The key secondary endpoints will not be tested if final OS is not met however, the results will be presented descriptively including 95% CI and the nominal p-value.

A table summarizing the results of the Hochberg closed test procedure will be provided indicating the applicable alpha level used.

Key secondary endpoints subject to Type I error control:

1. RECIST response: ORR and DCR
2. Time to SSE

Time to Symptomatic Skeletal Event

Time to SSE (defined in Section 8.1.2) will be summarized and analyzed in the same manner as described for rPFS (both primary and supportive analyses using the alpha levels and confidence intervals as described in the table above) using the PFS-FAS, except using 2-sided p-values from the stratified log-rank test as the primary comparison. An additional analysis will be done on the FAS population using the same methods as for the primary analysis.

Overall Response and Disease Control Rate

Percent change of sum of diameters of target lesions (in mm) from baseline per independent central review will be summarized as follows:

- Continuous variable summaries of baseline and best % change from baseline

Overall response rate and disease control rate per independent central review (defined in Section 8.1.2) will be analyzed using logistic regression with a single covariate for randomized treatment arm and stratification for the randomization stratification factors. The following will be reported:

- Odds ratio (active: control) with CI as described in the table above
- The associated 2-sided p-value
- DOR will be displayed using Kaplan-Meier curves, median, 25th percentile, and 75th percentile with 95% CIs, number (%) events and censored, and will be analyzed using mixture distribution methodology (Ellis et al. 2008) outlined below.

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The primary analysis of RECIST ORR and DCR will be on the Response Evaluable Analysis Set.

Mixture distribution analysis for duration of response

Duration of Response (DOR) per independent central review will be analyzed in the Response Evaluable Analysis Set using mixture distribution methodology (Ellis et al. 2008). To avoid an inflated estimate of duration of response that occurs when estimating only in the subset of patients that have a response, the following methods, paraphrasing from Ellis et al., will be used. Treatment arm differences in duration of response will be analyzed using a mixture distribution to test the hypothesis that the expected duration of response (EDoR) is equal for the experimental treatment, E, and the control treatment, C, that is:

$$H_0: R = EDoR_E/EDoR_C = 1 \text{ versus } H_a: R = EDoR_E/EDoR_C \neq 1 \quad (1)$$

The test will be performed as follows.

- (i) Estimate the proportions of patients with RECIST response as

$$p_E = r_E/N_E \text{ and } p_C = r_C/N_C \quad (2)$$

Where r_E and r_C are the number of patients responding to treatment arms E and C;

N_E and N_C are the number of all patients in each treatment arm.

(ii) Estimate the mean duration of response in each treatment arm, M_E and M_C , and their standard errors, using a time to event probability distribution, in responding patients, some of which may be censored in response. This can be done using SAS PROC LIFEREG for distributions such as the exponential, the Weibull, the gamma, the Normal, and the log Normal. The choice in the distribution will be made based upon overall data (ignoring randomized treatment arm) prior to the planned analysis after the database is locked.

(iii) Combine the estimates from step (i) and (ii) to calculate estimates of R and $\text{Var}[\ln(R)]$. Then assess the difference between treatment arms E and C using the test statistic:

$$z = \frac{\ln(\hat{R})}{\sqrt{\text{Var}[\ln(\hat{R})]}}$$

8.2.3 Additional Secondary Efficacy Analyses

Refer to Section 8.2 for analysis sets and presentation of summary statistics. The Additional Secondary Endpoints will be assessed and presented at the nominal 5% level, i.e., there will be no alpha control applied at the planned analyses as described in Section 4. These endpoints are PFS, Biochemical Response (PSA response endpoints, LDH and ALP assessments), Health-related QoL, and Health Economics. Analysis will be performed on the PFS-FAS population

8.2.3.1 Progression-free Survival Analysis

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PFS (defined in Section 8.1.3), will be summarized and analyzed in the same manner as those described for the alternate primary endpoint rPFS using the PFS-FAS, except using 2 sided p-values from the Cox regression model instead of the p-value from the Log-Rank test. Radiographic progressions per independent central review will be used. No sensitivity analyses will be performed for PFS. Additionally, the following will be presented:

- Number and % of PFS events that are due to death, radiographic progression, clinical progression (including the primary criteria of clinical progression), and PSA progression

8.2.3.2 Biochemical Response Analysis

All biochemical response analyses will be performed using the PFS-FAS. PSA, ALP, and LDH values will be summarized descriptively as follows:

- Continuous variable summary statistics for baseline, each time point, and % change from baseline for each treatment arm
- Plots of the mean (\pm standard error) values over time for PSA, ALP, and LDH.
- Summary statistics of PSA doubling time with 95% CI for the mean PSA doubling time
- Summary statistics of maximum % change from baseline
- Categorical variable summary statistics and 95% CIs of PSA response ($\geq 50\%$ decrease and PSA $\geq 80\%$ decrease)
- Waterfall plot of the maximum % change from baseline in PSA for each patient
- Duration of PSA response ($\geq 50\%$ decrease) will be presented descriptively the same as DOR (Section 8.2.2).

Unscheduled labs will not be included in tables but will be provided in listings.

Treatment arm differences of % change from baseline in PSA, ALP, and LDH across all time points will be analyzed using mixed effects general linear models for repeated measures, under the assumption of Missing at Random (MAR). The fixed effects will include treatment arm, time (as a categorical variable), treatment by time interaction, and randomization stratification factors. An unstructured variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of parameters of the model. If necessary for the model fit, the outcome variables might be transformed. Details of any transformations used will be provided in the CSR. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected time points will be presented.

For PSA response, analyses will be the same as those described for binary outcome ORR (Section 8.2.2).

Duration of PSA response will be analyzed using a mixture distribution analysis, as described for DOR (Section 8.2.2).

8.2.3.3 Quality of Life (QoL) Analysis

For QoL analyses, patient reported outcomes (PROs) will be assessed using the questionnaires EQ-5D-5L, FACT-P, and BPI-SF.

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Analyses will be done on the PFS-FAS, and all results will be reported by treatment arm. QoL measures are collected on Day 1 of each treatment cycle and at the EOT visit. Analyses over time will include time up through EOT visit.

For analysis of each outcome, only patients with a baseline value and at least one post baseline time point will be included. As with all efficacy analyses, main models will be adjusted for randomization stratification factors. Type I error is not controlled in the multiple health related QoL analyses. Thus, all p-values presented will be unadjusted and are nominal and descriptive.

8.2.3.3.1 EQ-5 Dimension-5 Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L is shown in protocol Appendix 9. The higher the EQ-VAS score, the better the QoL. The higher the EQ-5D items, the worse the QoL.

Description and Scoring

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale.

Each of the five dimension-scales contain five levels, with level 1 indicating no problems, level 2 indicating slight problems, level 3 indicating moderate problems, level 4 indicating severe problems, and level 5 indicating unable to/extreme problems.

The EQ-VAS is scored by assigning an integer value, ranging from 0 (Worst imaginable health state) to 100 (Best imaginable health state), corresponding to the mark placed by the patient on the VAS. Ambiguous answers (e.g., two marks placed on the scale by a patient) should be treated as missing values.

Scale name	Number of items	Item range*
Descriptive System Dimension		
Mobility	1	1-5
Self-Care	1	1-5
Usual Activities	1	1-5
Pain/Discomfort	1	1-5
Anxiety/Depression	1	1-5
Health State Evaluation		
EQ-VAS*	1	0-100

* EQ-VAS is a continuous visual analog scale, with integer scores ranging from 0 to 100.

A utility score will be obtained by using a weighted combination of the levels of the five dimension-scales. The weights are based on value sets which are country-specific. The country specific code for the U.K. will be used for all sites in this study since the health economics modeling will target the U.K. population for developing the core economic model. Each patient's 5 digit health states code (response to question 1,2,3,4, and 5

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concatenated (ex., 41325 results in a utility score of 0.193)) is converted to a utility score using the EQ-5D-5L value set, available in the cross-walk index value calculator which can be downloaded from the web site <https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation/crosswalk-index-value-calculator/>. (Scroll to the bottom of the web page and download the Excel file. Use the sheet labelled 'EQ-5D-5L Value Sets'.)

Since utility score depends on the combination of all items' responses, any missing response results in a missing utility score. If a patient dies, for analysis he will be assigned a score of 0 on the date of death. In the U.K. value set, utility scores ranges from the lowest possible score for a living patient of -0.594 (when all responses are '5') to 1 (when all responses are '1').

Analysis

For each of the five dimension-scales, frequency count and percentage of each reporting level (1 to 5) over time will be presented.

Utility score and EQ-VAS, will be summarized as continuous variables and will be presented for each time point. For EQ-VAS and Utility score, a plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed.

The proportion of patients and associated 95% CI who experience any improvement relative to baseline in utility score (an increase of .001 or more) at any time up through EOT will be summarized for each treatment.

Similarly, the proportion of patients with worsening relative to baseline, indicated by no change or any decrease in score, will be summarized.

Time to worsening for utility score is defined as the time (in months) from randomization to the first occurrence of worsening in score relative to baseline (no change or any decrease), clinical disease progression (excluding radiographic and PSA progression), or death, whichever is earlier. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival curves for the time to worsening (months) for each treatment arm will be computed using the Kaplan-Meier method. The two treatment arms will be compared using a cox regression analysis stratified for randomization stratification factors (LDH \leq 260 UI/L vs \geq , liver metastases (yes vs no), ECOG (0-1 vs 2), Inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no)). The 25th percentile of and median time to worsening will be presented, in case less than 50% of subjects experienced worsening for some variables.

Change from baseline in utility score will also be analyzed using general linear models for repeated measures. Baseline value (as a continuous variable), treatment arm, time (as visit number), treatment by time interaction, baseline by time interactions, and randomization stratification factors as main effects will be the fixed factors. A general (unstructured) variance-covariance matrix for the repeated measures for a single patient will be used. In case of problems with fitting the model, as an alternative, a heterogeneous Toeplitz and AR(1) structures will be considered to reduce the number of the parameters of the model. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected time points will be presented.

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8.2.3.3.2 FACT-P

The Functional Assessment of Cancer Therapy – Prostate (FACT-P) is shown in protocol Appendix 10. The higher the FACT-P score (for all subscales and total scales), the better the QoL.

Description

Scale/Sub-scale Name	Number of Items	Scale Range	FACT-P Item numbers	Threshold for worsening*
Subscale				
Physical Well-Being (PWB)	7 items	0-28	GP1-GP7	3
Social/Family Well-Being (SFWB)	7 items	0-28	GS1-GS7	3
Emotional Well-Being (EWB)	6 items	0-24	GE1-GE6	3
Functional Well-Being (FWB)	7 items	0-28	GF1-GF7	3
Prostate Cancer Subscale (PCS)	12 items	0-48	All items in "Additional Concerns" section	3
PCS pain-related subscale (PRS)	4 items	0-16	P1, P2, P3, GP4	2
FACT Advanced Prostate Symptom Index-8 (FAPSI-8)**	8 items	0-32	GP1, GP4, GE6, C2, P2, P3, P7, P8	3
Total Scale				
Trial Outcomes Index (TOI) score	3 subscales	0-104	PWB, FWB, PCS	9
FACT-G (General)	4 subscales	0-108	PWB, SFWB, EWB, FWB	9
FACT-P Total	39 items	0-156	All	10

*Minimally important difference for both 1) decrease from baseline for within subject change and 2) between group differences for treatment comparisons.

** Symptom index of important clinician-rated symptoms/concerns to monitor when assessing value of treatment for advanced prostate cancer (FAPSI-8; Yount et al. 2003)

Scoring

Scoring of FACT-P subscales and total scores (Trial Outcome Index (TOI), FACT-G Total Score (G for general), and FACT-P Total Score (P for prostate)) are shown below. These are from the FACT-P Scoring Guidelines (Version 4). Item codes in scoring guidelines are shown on the FACT-P form in Appendix 10 of the protocol.

FACT-P Instructions:

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- 1) Record answers in "item response" column. If missing, mark with an X
- 2) Perform reversals as indicated, and sum individual items to obtain a score.
- 3) Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
- 4) Add subscale scores to derive total scores (TOI, FACT-G, FACT-P).
- 5) **Handling missing items.** The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 32 of 39 FACT-P items completed). In addition, a total score should only be calculated if ALL of the component subscales have valid scores. For subscales, as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), prorate the subscale score by following the scoring instructions below, producing an observed sum weighted by the inverse of the proportion of observed items.

Subscale	Item Code	Reverse item?	Item response	Item Score
Physical Well-Being (PWB)	GP1	4	-	=
	GP2	4	-	=
	GP3	4	-	=
	GP4	4	-	=
	GP5	4	-	=
	GP6	4	-	=
	GP7	4	-	=
Sum individual item scores: Multiply by 7: Divide by number of items answered:				= PWB subscale score
Social/Family Well-Being (SFWB)	GS1	0	+	=
	GS2	0	+	=
	GS3	0	+	=
	GS4	0	+	=
	GS5	0	+	=
	GS6	0	+	=
	GS7	0	+	=
Sum individual item scores: Multiply by 7: Divide by number of items answered:				= SFWB subscale score
Emotional Well-Being (EWB)	GE1	4	-	=
	GE2	0	+	=
	GE3	4	-	=
	GE4	4	-	=
	GE5	4	-	=
	GE6	4	-	=
	Sum individual item scores: Multiply by 6: Divide by number of items answered:			
Functional Well-Being (FWB)	GF1	0	+	=
	GF2	0	+	=
	GF3	0	+	=
	GF4	0	+	=
	GF5	0	+	=
	GF6	0	+	=
	GF7	0	+	=
Sum individual item scores: Multiply by 7: Divide by number of items answered:				= FWB subscale score

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Subscale	Item Code	Reverse item?	Item response	Item Score
Prostate Cancer Subscale (PCS)	C2	4 -		=
	C6	0 +		=
	P1	4 -		=
Score range: 0-48	P2	4 -		=
	P3	4 -		=
	P4	0 +		=
	P5	0 +		=
	P6	4 -		=
	P7	4 -		=
	BL2	4 -		=
	P8	4 -		=
	BL5	0 +		=
<i>Sum individual item scores:</i>				
<i>Multiply by 12:</i>				
<i>Divide by number of items answered:</i>				
<i>= PC Subscale score</i>				

To derive a FACT-P Trial Outcome Index (TOI):

Score range: 0-104

$$\frac{(\text{PWB score})}{(\text{PWB score})} + \frac{(\text{FWB score})}{(\text{FWB score})} + \frac{(\text{PCS score})}{(\text{PCS score})} = \underline{\hspace{2cm}} = \text{FACT-P TOI}$$

To derive a FACT-G Total score:

Score range: 0-108

$$\frac{(\text{PWB score})}{(\text{PWB score})} + \frac{(\text{SFWB score})}{(\text{SFWB score})} + \frac{(\text{EWB score})}{(\text{EWB score})} + \frac{(\text{FWB score})}{(\text{FWB score})} = \underline{\hspace{2cm}} = \text{FACT-G Total score}$$

To derive a FACT-P Total score:

Score range: 0-156

$$\frac{(\text{PWB score})}{(\text{PWB score})} + \frac{(\text{SFWB score})}{(\text{SFWB score})} + \frac{(\text{EWB score})}{(\text{EWB score})} + \frac{(\text{FWB score})}{(\text{FWB score})} + \frac{(\text{PCS score})}{(\text{PCS score})} = \underline{\hspace{2cm}} = \text{FACT-P Total score}$$

To derive Pain-related subscale (PRS):

Subscale	Item Code	Reverse item?	Item response	Item Score
Pain-related subscale	P1	4 -		=
	P2	4 -		=
	P3	4 -		=
Score range: 0-16	GP4	4 -		=
<i>Sum individual item scores:</i>				
<i>Multiply by 4:</i>				
<i>Divide by number of items answered:</i>				
<i>= PR Subscale score</i>				

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To derive FACT Advanced Prostate Symptom Index-8 (FAPSI-8):

Using the 8 items GP1, GP4, GE6, C2, P2, P3, P7, P8, do the following:

Reverse code individual items as needed following guidelines in scores above.

Sum individual item scores.

Multiply by 8.

Divide by the number of items answered.

Analysis

For each FACT-P related total scale and subscale described in the table in the Description section above, will be summarized as continuous variables and will be presented for each time point. A plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed for FACT-P total scale only.

Subscale analysis criteria:

When a treatment difference in the time to worsening in FACT-P total score results in a $p < 0.05$, the FACT-P total subscales defined above (PWB, SFWB, EWB, FWB, PCS) will be analyzed to determine which are associated with the differences.

The proportion of patients that experience improvement relative to baseline in FACT-P total score indicated by a ≥ 10 point increase at any time up through EOT will be summarized as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

The proportion of patients that experience worsening relative to baseline in FACT-P total score indicated by a ≥ 10 point decrease will be summarized similarly.

Time to worsening for FACT-P total score is defined as the time (in months) from randomization to the first occurring of a ≥ 10 point decrease in FACT-P compared to baseline, clinical disease progression (excluding radiographic and PSA progression), or death. If no event is experienced, the censoring date will be time of the last QoL assessment.

Survival analyses will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales when the .05 criteria described above is met.

Change from baseline in FACT-P total score will also be analyzed using general linear models for repeated measures produced as described in Section 8.2.3.3.1 for EQ-5D-5L utility score, and subsequently for the subscales (PWB, SFWB, EWB, FWB, PCS) when the .05 criteria described above is met.

The same analyses as described for FACT-P total score will be performed for the PRS, FAPSI-8, TOI, and FACT-G, except using the appropriate threshold values as defined in the Description table above and plots for TOI and FACT-G only. No subscale analyses will be performed if $p < 0.05$.

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8.2.3.3.3 BPI-SF

The Brief Pain Inventory - Short Form (BPI-SF) is shown in protocol Appendix 8. The higher the BPI-SF score, the worse the pain.

Description and Scoring

The BPI-SF consists of 4 questions regarding pain intensity, 2 questions on the use of analgesics, and 7 questions on how the level pain has interfered with the subject's life. Intensity items consist of an 11-response rating scale scored from 0 ("No Pain") to 10 ("Pain As Bad As You Can Imagine"). Interference items consist of scores from 0 ("Does Not Interfere") to 10 ("Completely Interferes").

Scale Name	Number of Items	Scale Range	BPI-SF Item numbers	Threshold for worsening*
Individual Item Scales				
Worst pain intensity	1	0-10	3	Either of ≥30% of baseline or ≥2-point increase**
Least pain intensity	1	0-10	4	
Average pain intensity	1	0-10	5	
Pain intensity right now	1	0-10	6	
Summary Scales				
Pain Intensity Scale	4	0-10	3-6	≥30% of baseline
Pain Interference Scale	7	0-10	9a-9g	≥30% of baseline

*Minimally important difference for both 1) increase from baseline for within subject change and 2) between group differences for treatment comparisons.

**Analysis of worst pain intensity is included in Section 8.2.3.4 Health Economics Analysis as time to disease related pain (TDRP).

BPI-SF Intensity is the mean of non-missing items of the 4 items in the table above, if there are 3 or more items not missing; otherwise this scale is set to missing.

BPI-SF Interference scale is the mean of non-missing items of the 7 items in the table above, if there are 4 or more items not missing; otherwise this scale is set to missing.

Analysis

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The Pain Intensity Scale, Pain Interference Scale, and the four individual pain intensity items in the table above, will be summarized as continuous variables and will be presented for each time point. A plot of the mean values with standard errors by treatment group at each time point (showing number of subjects at each visit), will be constructed for Pain Intensity Scale, Pain Interference Scale and Worst Pain Intensity Scale, only.

Time to worsening of Worst Pain Intensity (item 3), also called Time to Disease Related Pain (TDRP), Pain Intensity Scale, and Pain Interference Scale are defined as the time (in months) from randomization to the first occurring of 1) an increase of worsening threshold (in the table above) compared to baseline, 2) clinical disease progression (excluding radiographic and PSA progression), or 3) death. If no event is experienced, the censoring date will be time of the last BPI-SF assessment.

Survival analyses of time to worsening of Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will be conducted as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

Additionally, the time to improvement following initial pain worsening in Pain Intensity Scale and Pain Interference Scale will be analyzed using mixture distribution methodology described in Section 8.2.2. Time to pain improvement is defined as time from worsening of intensity or interference to a score \leq baseline.

Change from baseline in Worst Pain Intensity, Pain Intensity Scale, and Pain Interference Scale will also be analyzed using general linear models for repeated measures as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

8.2.3.4 Health Economics Analysis

The health economics analysis will be done by a separate vendor and is not a part of this SAP; however, data relating to health resource utilization, feeding into the health economics analysis, will be summarized using the PFS-FAS as described in this section. All data relating to health resource utilization will be listed.

Health resource utilization data will be used to support health economic evaluations. Study specific analyses will focus on descriptive statistics of the variables described below occurring during the randomized treatment period and will be summarized by treatment arm as described in Section 5 for categorical and continuous variables.

Survival analyses of time to disease-related pain and time to first use of opioid analgesics will be conducted similarly as described in Section 8.2.3.3.1 for EQ-5D-5L utility score.

1. Hospital admissions

- Number of hospitalizations both as a categorical variable and a continuous variable
- Hospitalizations (yes/no) (admitted as in-patient)
- LOS per hospitalization episode will be estimated and the total LOS in the hospital per patient will be summarized.
- Total Number of symptomatic skeletal events (SSEs; includes symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to

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relieve bone pain; captured in 3 CRFs: Adverse Events, Concurrent Surgical/Therapeutic Procedures, and Radiotherapy)

- Number of hospitalizations for SSEs
- 2. Duration of time in hospital following ^{177}Lu -PSMA-617 administration (hours) is the time span of patient discharge as captured on the ^{177}Lu -PSMA-617 administration CRF.
- 3. Concomitant drug category use (frequency of administration, dose (listed only); total number of days administered = end date-start date + 1). The list of concomitant drugs as captured on the concomitant medication/therapy CRF page to include in each category will be pre-specified and flagged prior to the pre-planned analyses.
 - (1) Bisphosphonates (including but not limited to zoledronic acid, alendronic acid, etc.), denosumab, and other bone targeted therapies)
 - (2) Corticosteroids for systemic use
 - (3) Antifungals for systemic use (i.e. ketoconazole)
 - (4) ESA (erythropoietin stimulating agents, i.e. epoetin alfa)
 - (5) Granulocyte macrophage colony-stimulating factor (GM-CSF)
 - (6) Novel androgen axis drugs (NAADs; i.e. enzalutamide, abiraterone, apalutamide)
 - (7) Antiemetics
 - (8) Opioid analgesics use for cancer-related pain
 - 1. Time to disease-related pain (TDRP or Time to worsening of Worst Pain Intensity as defined in Section 8.2.3.3.)
 - 2. Time to first use of opioid analgesics (TFOA, defined below)
- 4. Therapeutic interventions (frequency; total number of days administered = end/stop date – start date + 1)
 - Local external beam radiotherapy, including palliative external radiation as captured on the concurrent radiotherapy CRF page.
 - Blood transfusion (full blood or derivates). The list of concomitant blood transfusions captured on the concomitant medication/therapy CRF page to include will be pre-specified and flagged prior to the pre-planned analyses.

Variable definitions:

Time to first use of opioid analgesic (TFOA) – TFOA is defined as days from randomization to the first occurrence of first need of pain and opioid analgesic use (OAU) as indicated in concurrent medications), clinical disease progression (excluding radiographic and PSA progression), or death. If no event is experienced, censoring date is the later of date of last visit and last concomitant medication recorded.

8.2.4 Sub-study

At the time of the final analysis of cumulative safety data of the sub-study patients (Section 4.2), limited efficacy data (excluding patient reported outcomes) will be summarized

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descriptively (i.e. no hypothesis testing will be performed) for the ¹⁷⁷Lu-PSMA-617+BSC/BSoC arm using the Sub-study Safety Analysis Set.

9. Safety Evaluation

Safety analyses will be presented using the PSMA-11 Safety Analysis Set or the FAS Safety Analysis Set except for study drug exposure (specifics in Section 9.1), ⁶⁸Ga-PSMA-11 adverse events (PSMA-11 Safety Analysis Set only), randomized treatment adverse events and adverse events during long-term follow-up (FAS Safety Analysis Set only) and prior/concurrent/post-therapies (specifics in Section 9.5, 9.6 and 9.7). Safety analyses of laboratory values and vital signs using the PSMA-11 Safety Analysis Set will only include assessments done at screening.

For the PSMA-11 and FAS safety analysis sets, tables will show results by treatment arm and for all patients combined. For the PSMA-11 Safety Analysis Set, an additional column will be included for patients not enrolled (i.e. not randomized).

Listings will be created by treatment arm.

9.1 Extent of Exposure

⁶⁸GA-PSMA-11 Exposure

For the PSMA-11 Safety Analysis Set, the variables to be summarized for ⁶⁸GA-PSMA-11 exposure are:

- ⁶⁸GA-PSMA-11 activity injected-decay corrected dose (MBq)
- ⁶⁸GA-PSMA-11 activity injected-decay corrected dose per body weight (MBq/kg)

Randomized Treatment Exposure, Summary of Cycles

For the FAS Safety Analysis Set, summary of treatment cycles variables to be included are:

Randomized treatment exposure, for both treatment arms:

- Duration of exposure to randomized treatment (months) (definition in Section 5.6)
- Number of cycles started per patient (both as categorical and continuous variable)
- Average duration of randomized treatment cycles (months) (definition in Section 5.6)
- Number of patients with at least one cycle delayed
- Number of cycles delayed with reasons for delay

¹⁷⁷Lu-PSMA-617 exposure, for the Lu-PSMA-617 + BSC/BSoC arm:

- Number of patients with at least one dose interrupted (omitted) with the reasons for interruption overall and by cycle
- Number of patients with at least one dose reduced with the reasons for dose reduction overall and by cycle

Randomized Treatment Exposure, By Cycle and Across Cycles Combined

¹⁷⁷Lu-PSMA-167 exposure, for the Lu-PSMA-617 + BSC/BSoC arm

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For the FAS Safety Analysis Set investigational treatment arm, ¹⁷⁷Lu-PSMA-167 exposure variables to be summarized (definitions in Section 5.6) are:

- Cumulative dose (GBq) of patient for the entire study overall
- Dose intensity per cycle (GBq/cycle) for each cycle
- Dose intensity (GBq/month) for the entire study overall
- Relative cycle dose intensity (%) for each cycle
- Relative dose intensity (%) for the entire study overall

BSC/BSoC exposure, for both treatment arms

For the FAS Safety Analysis Set (both treatment arms), variables to be tabulated for BSC/BSoC for the entire study and for each treatment cycle are:

- Concomitant medications indicated as study BSC/BSoC, coded using WHO Drug Global dictionary. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings. A pre-specified list of concomitant medications, based on the interventions allowed as BSC/BSoC per protocol (protocol section 5.2) will be used to indicate and flag concomitant medications as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will not be used to identify concomitant medications indicated as study BSC/BSoC.
- Concurrent procedures other than radiotherapy indicated as study BSC/BSoC, coded using MedDRA. The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings. The BSC/BSoC flag captured on the CRF will be used to identify concurrent procedures other than radiotherapy indicated as study BSC/BSoC.
- Concurrent radiotherapy indicated as study BSC/BSoC. The BSC/BSoC flag captured on the CRF will be used to identify concurrent radiotherapy indicated as study BSC/BSoC.

Additionally, a summary of the number (%) of patients who received a NAAD as study BSC/BSoC, type of NAAD received (by WHO Drug preferred name) and duration of exposure will be provided by treatment arm and overall using the FAS Safety Set. All concomitant medications, concurrent procedures and radiotherapies flagged as study BSC/BSoC will be listed.

9.1.1 Sub-study

⁶⁸GA-PSMA-11 exposure will be summarized using the PSMA-11 Sub-study Analysis Set. Study treatment and ¹⁷⁷Lu-PSMA-617 exposure will be summarized as described above using the Sub-study Safety Analysis Set.

9.2 Adverse Events and Deaths

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC) and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE criteria [v5.0]). The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

9.2.1 Definition of Treatment Emergent Adverse Events (TEAEs)

⁶⁸GA-PSMA-11

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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 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 prior to Cycle 1 Day 1 for the BSC/BSoC arm.

AEs 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 AEs that occur beyond 6 days will not be TEAEs.

Randomized treatments

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 BSC/BSoC 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 initiation of randomized treatment up to 30 days after the date of the last administration of randomized treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

9.2.2 General Convention

Any treatment-emergent event as defined in Section 9.2.1 missing the assessment of relatedness will be considered study drug-related.

In case a patient experienced the same event more than once, the maximum toxicity grade will be presented.

In all AE tables except the ones presented by Cycles, multiple occurrences of the same adverse events occurring in one individual are counted only once.

In all AE tables presented by cycle of onset, multiple occurrences of the same adverse events occurring in one individual within one cycle are counted only once.

AE summaries for ^{68}GA -PSMA-11 and Randomized Treatment will include AEs occurring during the treatment-emergent period whereas AE summaries for Long-term Follow up will include new and existing AEs during the long-term follow-up period captured on the Long-Term Follow up CRF page. All AEs will be listed along with the information collected on those AEs. AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. The total number of events will also be provided. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE toxicity grades for the same preferred term will be summarized under the maximum CTCAE toxicity grade recorded for the event. AE with missing CTCAE toxicity grade will be included in the total across all grades of the summary table.

In all AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the ^{177}Lu -PSMA-617+BSC/BSoC arm for randomized treatment and long-term follow-up AE summaries and the frequency in the overall column for ^{68}Ga -PSMA-11 AE summaries.

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9.2.3 ^{68}Ga -PSMA-11 Adverse Events

A summary table using the PSMA-11 Safety Analysis Set including the number of patients with at least one event, and the total number of events will be presented for the following variables:

- TEAE¹
- serious TEAE¹
- grade 3/4/5 TEAE²
- drug-related TEAE¹
- serious drug-related TEAE¹
- drug-related grade 3/4/5 TEAE²
- fatal TEAE²

¹AE variables to be tabulated by SOC and PT by grade including a total across all grades and all grades 3/4/5.

²AE variables to be tabulated by SOC and PT.

A summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

A listing will include the participant identifier, age, race, verbatim, preferred term, duration of the event, toxicity grade, seriousness, action taken regarding ^{68}Ga -PSMA-11, outcome, relationship to study drug, and start and end date. Non-treatment-emergent adverse events will be flagged.

9.2.3.1 Sub-study

Similar analyses as described in Section 9.2.3 will be done using the PSMA-11 Sub-study Analysis Set.

9.2.4 Randomized Treatment Adverse Events

A summary table using the FAS Safety Analysis Set including the number of patients with at least one event, and the total number of events will be presented for the AE variables below.

- TEAE^{1, 3}
- Serious TEAE^{1, 3}
- Grade 3/4/5 TEAE²
- Drug-related TEAE¹
- Serious drug-related TEAE¹
- Drug-related grade 3/4/5 TEAE²
- TEAE leading to reduction of ^{177}Lu -PSMA-617 dose¹ or of BSC/BSoC¹
- TEAE leading to interruption of ^{177}Lu -PSMA-617 treatment¹ or of BSC/BSoC¹
- TEAE leading to permanent discontinuation of ^{177}Lu -PSMA-617 treatment¹ or of BSC/BSoC¹
- Fatal TEAE²

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¹AE variables to be tabulated by SOC and PT by grade (including a total across all grades and all grades 3/4/5).

²AE variables to be tabulated by SOC and PT.

³TEAEs are to be tabulated by SOC and PT, including a total across all grades and all grades 3/4/5), and by ¹⁷⁷Lu-PSMA-167 cycle of onset.

A summary of serious and non-serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

A listing for each patient will include the same variables as mentioned above in Section 9.2.3 except will include action taken regarding ¹⁷⁷Lu-PSMA-617 and action taken regarding Best supportive/Best standard of care. Non-treatment-emergent adverse events will be flagged.

To help evaluate the impact of the COVID-19 virus on the safety, the incidence of COVID-19 related adverse event preferred terms will be presented incorporating (a) COVID-19 related adverse events with an onset date prior to the start of the outbreak (i.e. pre-2020) and (b) all COVID-19 related adverse events occurring before the data cut-off. All COVID-related AEs will be included in the listings.

9.2.4.1 Sub-study

Similar analyses as described in Section 9.2.4 (excluding TEAEs by ¹⁷⁷Lu-PSMA-167 cycle of onset due to the small number of patients) will be performed using the Sub-study Safety Analysis Set. All AEs will be listed including COVID-related AEs.

9.2.5 Deaths

Summaries of all deaths, including deaths within 6 weeks and 3 months (12 weeks) of randomization (using the FAS and FAS Safety Set), on-treatment deaths or within 30 days of randomized treatment discontinuation (using the FAS Safety Set), and ⁶⁸Ga-PSMA-11 on-treatment deaths (using the PSMA-11 Safety Analysis Set) will be provided including the primary cause of death (including deaths due to COVID-19). All deaths will be listed and will include the details for 'other cause'.

9.2.5.1 Sub-study

A summary of all deaths and on-treatment deaths will be provided using the Sub-study Safety Analysis Set. A summary of ⁶⁸Ga-PSMA-11 on-treatment deaths will be provided using the PSMA-11 Sub-study Analysis Set. All deaths in the sub-study will be listed.

9.2.6 Long-term Follow up Adverse Events

During LTFU, new and existing AEs will continue to be followed, capturing only AE term and grade.

A summary table including the number of patients with at least one event, and the total number of events will be presented for the AE variables captured on the Long Term Follow-Up – Adverse Events CRF page below using the FAS Safety Analysis Set.

- AE¹
- Grade 3/4/5 AE²
- Fatal AE²

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¹AE variables to be tabulated by SOC and PT by grade including a total across all grades and all grades 3/4/5.

²AE variables to be tabulated by SOC and PT.

A listing will include the participant identifier, age, race, verbatim, preferred term, and toxicity grade.

9.2.6.1 Sub-study

A listing of all AEs captured during long-term follow up will be provided.

9.2.7 Safety Topics of Interest

A safety topic of interest is a grouping of adverse events that are of scientific and medical concern specific to ⁶⁸Ga-PSMA-11 and ¹⁷⁷Lu-PSMA-617. These groupings are defined on a program level using MedDRA terms, SMQs (standardized MedDRA queries), HLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) document and will be summarized. The latest version of the CRS document available at the time of the analyses will be used. For each specified safety topic of interest, number and percentage of patients with at least one event of the safety topic of interest occurring during the on treatment period will be summarized.

Summaries of these Safety Topics of Interest during ⁶⁸Ga-PSMA-11 treatment period (using PSMA-11 Safety Analysis Set) and during randomized treatment period (using the FAS Safety Analysis Set) will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation (if applicable), leading to dose interruption (if applicable), hospitalization, death etc.).

A listing of all grouping levels down to the MedDRA preferred terms used to define each Safety Topic of Interest will be generated.

9.2.7.1 Sub-study

A listing of Safety Topics of Interest during ⁶⁸Ga-PSMA-11 treatment period (using PSMA-11 Sub-study Analysis Set) and during ¹⁷⁷Lu-PSMA-617 treatment period (using the Sub-study Safety Analysis Set) will be provided.

9.3 Clinical Laboratory Determination

Local labs will perform hematology, chemistry, serum testosterone, and urinalysis testing. The following laboratory parameters are to be summarized:

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• Testosterone			
• Chemistry	sodium potassium total and direct bilirubin ALP AST ALT	LDH blood urea nitrogen ² creatinine urate phosphate chloride	Bicarbonate ¹ calcium glucose total protein albumin
• Urinalysis ³	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		

1. total carbon dioxide or equivalent is acceptable
2. urea is acceptable

3. Urinalysis parameters are only collected at screening. Appearance and color, glucose, ketones and protein content are captured as free-text and will only be listed (not summarized).

Hematology, chemistry and serum testosterone laboratory values and the change from baseline during randomized treatment will be summarized for each parameter by visit. Shift tables of the worst post-baseline on-treatment laboratory toxicity based on CTCAE v5.0 grading relative to baseline will be presented as well as the frequency of grade 3/4 toxicities. For laboratory tests where CTCAE grades are not defined, shift tables using low/normal/high/(low and high) classification to compare baseline to worst post-baseline on-treatment value will be presented. Frequency statistics for qualitative laboratory parameters will also be presented by visit. The summaries will include all laboratory assessments collected no later than 30 days after the last administration of randomized treatment (i.e. on-treatment).

The mean (\pm standard error) values over time will be plotted for hemoglobin, hematocrit, platelets, WBC, absolute neutrophil count, AST, ALT, BUN, and creatinine by treatment arm.

An additional summary of hematology, chemistry and serum testosterone laboratory values at screening will be provided for the PSMA-11 Safety Analysis Set.

Listings of all laboratory data and listings of laboratory toxicities \geq Grade 3 will be provided. Values outside of the laboratory's reference range will be flagged. Values collected later than 30 days after the last randomized treatment date will also be flagged. If laboratory values are provided as ' $<X$ ' (i.e. below limit of detection) or ' $>X$ ', prior to conversion of laboratory values to SI unit, these numeric values are set to X. The patient listings will indicate the CTCAE grade.

During long-term follow up, hematology and chemistry are collected every 3 months. Shift tables of the worst post-baseline laboratory toxicity during LTFU based on CTCAE v5.0

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grading relative to baseline will be presented as well as the frequency of grade 3/4 toxicities. For laboratory tests where CTCAE grades are not defined, shift tables using low/normal/high/(low and high) classification to compare baseline to worst post-baseline value during LTFU will be presented. These will be displayed in similar tables separately for LTFU using the FAS Safety Analysis Set. Laboratory assessments collected during LTFU will be included in the listings.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values will be summarized by treatment arm using the FAS Safety Analysis Set only. The following summaries will be produced during the randomized treatment and long-term follow up, separately:

- ALT > 3xULN
- ALT > 5xULN
- ALT > 8xULN
- ALT > 10xULN
- ALT > 20xULN
- AST > 3xULN
- AST > 5xULN
- AST > 8xULN
- AST > 10xULN
- AST > 20xULN
- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- Concurrent ALT > 3xULN & TBL > 2xULN
- Concurrent AST > 3xULN & TBL > 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN
- Concurrent ALT or AST > 3xULN & TBL > 2xULN & ALP ≥ 2xULN

For single parameters (e.g. AST>3xULN), the worst value post-baseline is considered. For the combination of various parameters, the lab values need to be from the same assessment (concurrent assessment). Concurrent measurements are those occurring on the same date. In addition, a listing of all TBL, ALT, AST and ALP values for subjects with a post-baseline TBL > 2xULN, ALT> 3xULN or AST > 3xULN will be provided using the FAS Safety Analysis Set. Values meeting the criteria during randomized treatment and LTFU will be listed.

9.3.1 Sub-study

Shift tables as described above will be presented using the Sub-study Safety Analysis Set. Listings of all laboratory data will be provided using the PSMA-11 Sub-study Analysis Set. Hematology and chemistry data collected during long-term follow up will be listed using the Sub-study Safety Analysis Set.

9.4 Vital Signs, Physical Findings, and ECG

Vital signs (blood pressure, pulse, and respiratory rate) and weight, will be summarized by visit (observed and change from baseline during randomized treatment). The summaries will include all assessments collected no later than 30 days after the last

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administration of randomized treatment (i.e. on-treatment). For those treated with ^{177}Lu -PSMA-617, the vital sign taken at 15 minutes pre-dose during the first 6 cycles will be used for the summary of changes by visit. The number (%) of patients with notable vital signs during randomized treatment (high/low) will be presented by treatment arm and overall using the FAS Safety Analysis Set. An additional summary of vital signs at screening will be provided using the PSMA-11 Safety Analysis Set. The clinically notable vital sign criteria are provide below:

Vital Sign (unit)	Clinically notable criteria	
	Above normal value	Below normal value
Weight (kg)	Increase > 10% from baseline	Decrease > 10% from baseline
Systolic blood Pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood Pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of >25%

ECOG performance status and change from baseline classified as improved, no change and worsened will be summarized as a categorical variable by visit for the FAS Safety Analysis Set only.

ECG will be done at screening only. Overall ECG interpretation will be summarized. PR, RR, and QRS Intervals and heart rate will be summarized as continuous variables. QTc, as captured on the CRF, will not be summarized as the correction method is site specific and will be recorded in the TMF. QTc will only be included in the listings with the correction method "unspecified." The number (%) of patients with notable ECG values at screening will also be presented using the PSMA-11 Safety Set and the FAS Safety Set:

Clinically notable ECG values	
HR	<ul style="list-style-type: none">Value of > 120 bpmValue of < 40 bpm
PR	<ul style="list-style-type: none">Value of > 200 ms
QRS	<ul style="list-style-type: none">Value of > 110 ms

Abnormal findings from physical examinations will be assessed for clinical significance and will be presented in the AE listings and tables as appropriate.

9.4.1 Sub-study

Notable vital signs (high/low) will be summarized using the Sub-study Safety Analysis Set. Vital signs will be listed using PSMA-11 sub-study analysis set. ECOG performance status will be listed using the Sub-study Safety Analysis Set. The analyses pertaining to the ECG data collected in the sub-study will be described in a separate SAP. These analyses will be performed by a separate vendor and are not part of this SAP.

9.5 Prior and Concurrent Surgical and Therapeutic Procedures

Prior and concurrent surgical and therapeutic procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized using the FAS Safety

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Set. The MedDRA version used for reporting will be specified as a footnote in the applicable tables and listings.

Procedures as captured on the Concurrent Surgical / Therapeutic Procedures CRF page will be classified as prior and/or concurrent. Prior procedures are all procedures occurring before the date of the first randomized drug administration (prior to first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concurrent procedures are all procedures continued or started on or after the date of the first randomized study drug administration but not more than 30 days after end of randomized treatment Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

Prior and concurrent surgical and therapeutic procedures will be tabulated separately by system organ class and preferred term. All procedures will be listed including all details from the concurrent surgical and therapeutic procedures CRF page.

9.5.1 Sub-study

Prior and/or concurrent surgical and therapeutic procedures during ¹⁷⁷Lu-PSMA-617+BSC/BSoC treatment period will be summarized using the Sub-study Safety Analysis Set.

9.6 Prior and Concurrent Radiotherapy

Descriptive statistics of prior and concurrent radiotherapy as captured on the Radiotherapy CRF page will be summarized using the FAS Safety Set. Prior radiotherapy are all radiotherapies occurring before the date of the first randomized drug administration (prior to first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concurrent radiotherapy are all radiotherapies that continued or started on or after the date of the first administration of randomized treatment but no more than 30 days after the end of randomized treatment. Assignment will be done after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

Prior and concurrent radiotherapy will be tabulated separately. The variables to be summarized in tables are:

- Number of patients with at least one prior (concurrent) radiotherapy
- Number of prior (concurrent) radiotherapies
- Unique Sites

All prior and concurrent radiotherapies recorded on the Radiotherapy CRF will be listed.

9.6.1 Sub-study

Prior and concurrent radiotherapy will be summarized using the Sub-study Safety Analysis Set.

9.7 Prior and Concomitant Medications

Prior and concomitant medications during the randomized treatment period will be coded using the WHO Drug Global dictionary and will be summarized using the FAS Safety Analysis Set. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings.

The medications as captured on the Concomitant Medication/Therapy CRF page will be classified as prior and/or concomitant during randomized treatment period. Prior medications are all medications taken before the date of the first randomized drug administration (prior to first dose of ¹⁷⁷Lu-PSMA-617 for the investigational arm and prior to Cycle 1 Day 1 for the BSC/BSoC arm). Concomitant medications are all medications continued or started on or after the date of the first randomized study drug administration but not more than 30 days after end of randomized treatment. Assignment will be done PSMA-617-01 SAP Version 3.0

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after applying the imputation rules as specified in Section 5.2 for partial start and end dates.

The number and percentage of patients will be tabulated by ATC level 4 and Preferred Term, by prior or concomitant medications during randomized treatment period.

Prior and concomitant medications during the ^{68}Ga -PSMA-11 dosing period will be summarized separately using the PSMA-11 Safety Analysis Set. Medications as captured on the Concomitant Medication/Therapy CRF page will be classified as prior and/or concurrent to ^{68}Ga -PSMA-11 dosing. Medications prior to ^{68}Ga -PSMA-11 dosing are all medications occurring before the date of ^{68}Ga -PSMA-11 dosing. Medications concurrent to ^{68}Ga -PSMA-11 dosing are all medications continued or started on or after the date of ^{68}Ga -PSMA-11 but not more than 6 days after administration or start of randomized treatment.

A listing of all medications recorded on the concomitant medications CRF page will provide details including flag for Best Supportive/Best Standard of Care, indication, dose, route, frequency, and start and stop dates.

9.7.1 Sub-study

Prior and/or concurrent medications during ^{177}Lu -PSMA-617+BSC/BSoC treatment period will be summarized using the Sub-study Safety Analysis Set. Prior and concomitant medications during the ^{68}Ga -PSMA-11 dosing period will be listed using the PSMA-11 Sub-study Analysis Set.

9.8 Post-Treatment Cancer-related Therapy

Drug or other non-radiation therapies will be classified according to WHO Drug Global dictionary and will be summarized using the FAS. The WHO Drug Global dictionary version used for reporting will be specified as a footnote in the applicable tables and listings.

The number and percentage of participants receiving a post-treatment cancer-related therapy since discontinuation of randomized treatment will be displayed by preferred term within each ATC. Post-treatment anti-cancer therapy summaries will be sorted alphabetically by preferred term within ATC class.

Best response to post treatment anti-cancer therapy and type of response will be summarized.

Descriptive statistics of post-treatment radiotherapy received after the randomized treatment period will be summarized. The variables to be summarized in tables are:

- Number of patients with at least one post-treatment radiotherapy
- Number of post-treatment radiotherapies
- Unique Sites

A listing of all data recorded on the post-treatment disease assessment, post-treatment radiotherapy, and post-treatment anti-cancer therapies CRFs will be provided.

9.8.1 Sub-study

Post-treatment cancer-related therapy since discontinuation of ^{177}Lu -PSMA-617+BSC/BSoC will be listed using the Sub-study Safety Analysis Set.

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Appendix A: Quality of Life Questionnaire References

References regarding EQ-5D-5L

Full scoring details for the EQ-5D-5L are described at the site https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

The derivation and performance of the value set for conversion of questionnaire responses to a utility score is described in the manuscript http://eprints.whiterose.ac.uk/121473/1/Devlin_et_al-2017-Health_Economics.pdf

Repeated measures analysis of PROs: Fitzmaurice G, et al., 2004. (full reference in Section 10)

References regarding the FACT-P

Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, version 4.0 (November 1997) is located on-line at www.facit.org

Minimally important differences in FACT-P related scales

Score type	Source	Total possible score	Range of MID	MID used in analyses
Physical well-being (PWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Social/family well-being (SFWB)	Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
Emotional well-being (EMB)	Yost et al. Eval Health Prof 2005; 28: 172-191	24	2-3	3
Functional well-being (FWB)	Cella et al. Qual Life Res 2002; 11: 207-221; Yost et al. Eval Health Prof 2005; 28: 172-191	28	2-3	3
FACT-G total score ^a	Cella et al. Value Health 2009; 12: 124-129	108		9
Prostate cancer subscale (PCS) score	Cella et al. Value Health 2009; 12: 124-129	48	2-3	3
FACT-P total score ^b	Cella et al. Value Health 2009; 12: 124-129	156	6-10	10
Pain-related subscale (PRS) ^c	Cella et al. Value Health 2009; 12: 124-129	16	1-2	2
TOI score	Yost et al. Eval Health Prof 2005; 28: 172-191	104	5-9	9
FAPSI-8	Cella et al. Value Health 2009; 12: 124-129	32	2-3	3

Notes: (a) Composite of the scores on the PWB+SFWB+EWB+FWB (b) Composite of the scores PWB+SFWB+EWB+FWB+PCS. Impaired QoL has been defined arbitrarily in published literature as a FACT-P score of ≤122-128, of the 156 maximum score (c) Calculated using the 4 questions on pain in the FACT-P, but the scores are reversed

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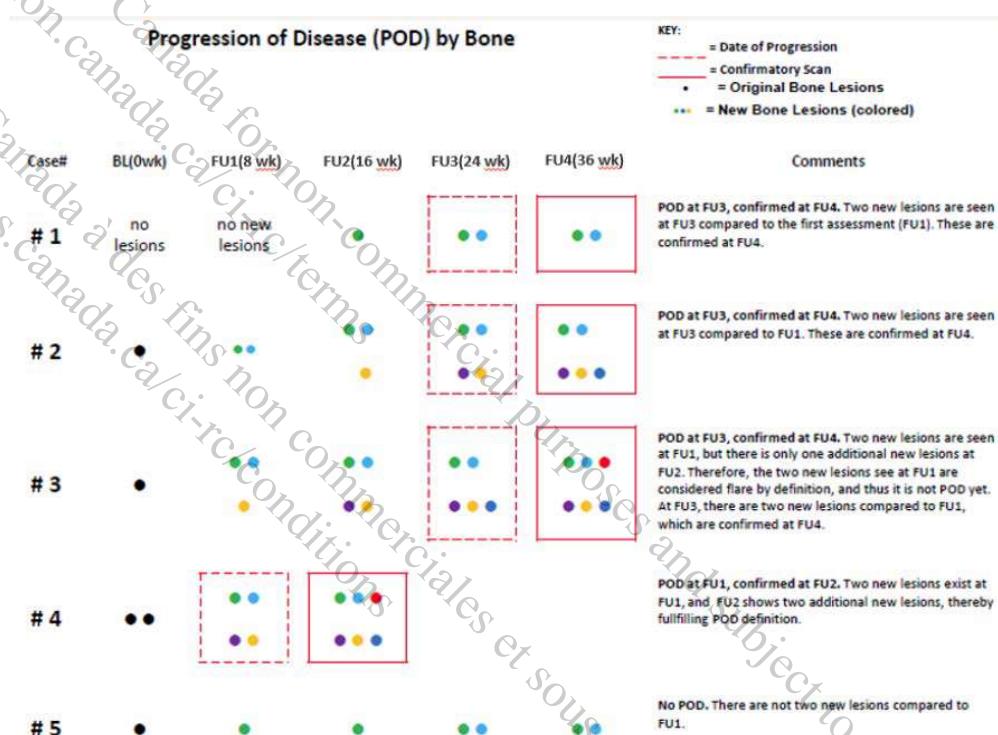
such that higher score indicates better health and less pain. A decrease in score signifies pain progression

Change thresholds for deterioration on the FACT-P PCS, TOI, and FACT-P Total scales are based upon Cella et al. 2009, which provided clinically meaningful change estimates in a prostate cancer sample based upon an anchoring methodology. The FACT-G scales (PWB, SFWB, EWB, FWB, and the FACT-G) were not addressed in that article, and so the clinically meaningful change estimates for those scales are derived from an earlier reference, which reports normative values from a large sample from the general population for the FACT-G scales. Standard errors (once normalized back to their original scales from the zero to 100 scale reported in the article) for the PWB, SFWB, EWB, FWB, and the FACT-G were 5.35, 6.80, 4.78, 6.83, and 18.04, respectively. Taking one half the standard deviation is equivalent to finding a 0.5 effect size. Using this distributional technique to find the clinically meaningful change estimates produced values of about 3 points for PWB, SFWB, EWB, and FWB and about 9 points for the FACT-G.

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Appendix B: Examples of Date of Bone Progression

Cases 1, 2 and 3 represent the date of bone progression by Rule 2 and Case 4 represents the date of bone progression by Rule 1, as described in Section 8.1.1. In Case 5, even though there are 2 new lesions compared to baseline at Week 24, there is only 1 new lesion compared to Week 8 thus indicating that there is no bone progression.



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Revision History

Version	Date	Revised by:	Changes
1.0	08 Jun 2018	[Name]	Original version
2.0	24 Oct 2019	[Name]	<p>Title page: Updated reviewers/approvers of SAP based on current SOP.</p> <p>Section 1: Updated the List of Abbreviations and Definitions of Terms based on current changes to document.</p> <p>Section 2: Updated protocol version and clarified that decisions will be made prior to database lock.</p> <p>Section 2.1: Revised based on changes reflected in protocol amendment v4.1 (e.g. updated Time to first SSE definition based on protocol amendment and clarified the analysis sets to be used for the key secondary endpoints).</p> <p>Section 3.1, 3.3 and 3.4: Revised based on changes reflected in protocol amendment v4.1 including the dosimetry, PK and ECG sub-study in Germany.</p> <p>Section 3.2: Minor clarifications on the type of randomization system used and who is blinded/unblinded. Added language indicating that patients enrolled into the sub-study will not be randomized.</p> <p>Section 3.3: Added additional secondary objective for the sub-study.</p> <p>Section 4 and 4.1: Revised based on changes reflected in protocol amendment v4.1. Section title revised.</p> <p>Section 5: Minor clarifications and updates including the adding the definition of time units. Added a definition for randomized treatment for the main study and the sub-study.</p> <p>Sections 5.1.1, 5.2, 6.2, 8.1 and 9.3: Minor clarifications and corrections.</p> <p>Section 5.1.2: Minor clarifications and corrections. Removed reference to Appendix A (Schedules of study Assessments) and added reference to protocol section and appendix.</p> <p>Section 5.3.1:</p>

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Version	Date	Revised by:	Changes
			<p>Revised based on changes reflected in protocol amendment v4.1. Added PFS Analysis Set and updated definition of the Response Evaluable Analysis Set.</p> <p>Section 5.3.2:</p> <p>Added two additional safety population: Sub-study Safety Analysis Set and PSMA-617 Safety Analysis Set.</p> <p>Section 5.4:</p> <p>Additional subgroup definitions were added.</p> <p>Section 5.4.1:</p> <p>Removed descriptive statistics at baseline summaries by subgroups. Clarified that subgroup analyses for efficacy will only be performed for rPFS and OS and removed analyses for secondary endpoints. Clarified which subgroups will be used for efficacy and safety analyses.</p> <p>Section 5.6:</p> <p>Minor clarifications and updates including: added definition for best % change, identified list of taxanes for Last taxane therapy treatment-free interval, and updated derivation and statistical model for PSA doubling time including applicable references.</p> <p>Section 6.1:</p> <p>Minor clarifications and corrections. Added summaries for screen failures, PFS Analysis Set, Sub-study Safety Analysis Set, enrollment by country and center and end of study status.</p> <p>Section 6.4:</p> <p>Added an additional summary of discordance between interactive response technology (IRT) system versus CRF collected stratification factors. Added PFS analysis set.</p> <p>Section 7:</p> <p>Minor clarifications and added PFS Analysis set. Added additional summaries for the Sub-study and PSMA-617 Safety Analysis Sets for section 7.1 and 7.2 only.</p> <p>Section 7.1:</p> <p>Minor clarifications including defining Age and Race groupings.</p> <p>Section 7.2:</p> <p>Minor clarifications including defining PSA doubling time groupings. Added summary of baseline Target and Non-Target Lesions.</p> <p>Section 7.3:</p>

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			<p>Minor clarifications and corrections. Removed version of MedDRA being used and added that the version will be specified in the applicable tables and listings.</p> <p>Section 7.4:</p> <p>Minor clarifications and corrections. Added definition for Duration of Therapy and Duration of historic BOR for (1) Last Taxane Therapy and (2) Last Therapy.</p> <p>Section 8.1.1:</p> <p>Revised based on changes reflected in protocol amendment v4.1. Moved sensitivity analyses to Section 8.2.1.</p> <p>Section 8.1.2:</p> <p>Minor clarifications on the key secondary efficacy definitions. Moved sensitivity analyses to Section 8.2.2.</p> <p>Section 8.1.3:</p> <p>Minor clarifications on the additional secondary efficacy definitions. Updated derivation and statistical model for PSA doubling time including applicable references.</p> <p>Section 8.2:</p> <p>Revised based on changes reflected in protocol amendment v4.1. Removed all unadjusted analyses. Added a statement that the stratification factors from the IRT system will be used for all analyses.</p> <p>Section 8.2.1:</p> <p>Revised based on changes reflected in protocol amendment v4.1. Updated statistical test model to use from stratified Cox model to stratified log-rank test, updated analysis set for rPFS and moved sensitivity analyses from Section 8.1.1 to this section. Added additional supportive analyses for rPFS and added text for subgroup analyses for rPFS and OS as referenced in Section 5.4.1. Added text for assessing proportionality assumption.</p> <p>Section 8.2.2:</p> <p>Revised based on changes reflected in protocol amendment v4.1. Minor clarifications on analysis sets to use for key secondary endpoint analyses, and the alpha level to use for the Hochberg closed test procedure.</p> <p>Section 8.2.3:</p> <p>Updated analysis set to be used.</p> <p>Sections 8.2.3.1, 8.2.3.2, 8.2.3.3 (including subsections) and 8.2.3.4:</p> <p>Minor clarifications including adding the statistical model to be used for time to improvement following initial pain</p>

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			<p>(Section 8.2.3.3.3), added duration of time in hospital following ^{177}Lu-PSMA-617 administration (section 8.2.3.4) and updated the analysis set to be used. Added waterfall plot for maximum % change from baseline in PSA (Section 8.2.3.2).</p> <p>Section 9:</p> <p>Clarified which analysis sets to use for the safety evaluation for the study (including sub-study).</p> <p>Section 9.1:</p> <p>Minor clarifications. Updated how the study BSC/BSoC will be flagged. Added new safety analysis sets due to addition of sub-study.</p> <p>Section 9.2:</p> <p>Minor clarifications and corrections. Added text that the version of MedDRA used will be specified in the applicable tables and listings.</p> <p>Section 9.2.1:</p> <p>Minor clarifications and corrections including updating the definition of the treatment emergent period for ^{68}Ga-PSMA-11.</p> <p>Section 9.2.2:</p> <p>Clarification on how AEs will be summarized and reported.</p> <p>Sections 9.2.3, 9.2.4 and 9.2.5:</p> <p>Analyses pertaining to deaths moved to Section 9.2.5.</p> <p>Section 9.2.5:</p> <p>Added section for summary of deaths.</p> <p>Section 9.4:</p> <p>Added definition of corrected QT using Fredericia's formula (QTcF) and clarified how QTc reported by site will be handled.</p> <p>Section 9.5:</p> <p>Minor clarifications and corrections. Indicated analysis sets to use for analyses. Removed version of MedDRA to be used and added that the version will be specified in the applicable tables and listings.</p> <p>Section 9.6:</p> <p>Added section on concurrent radiotherapy summaries.</p> <p>Section 9.7:</p> <p>Indicated analysis sets to use for analyses.</p> <p>Section 9.8:</p>

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			<p>Indicated analysis sets to use for analyses. Minor clarifications and corrections. Added post-treatment radiotherapy summaries.</p> <p>Section 10:</p> <p>Added additional references for PSA Doubling Time derivation.</p> <p>Appendices:</p> <p>Removed schedules of study assessments from Appendix A since the schedules can be found in the protocol. Minor clarifications and corrections to remaining appendices.</p>
3.0	18 Jan 2021	[Name]	<p>Changes needed for the final rPFS/interim and final OS analyses including analyses to describe and assess the impact of COVID-19. Analyses pertaining to the sub-study are now described in sub-sections rather than embedded as done in SAP v2.0. The following is a list of all changes since SAP v2.0:</p> <p>List of reviewers and approvers have been updated on title page due to personnel and title/role changes.</p> <p>Section 1 List of Abbreviations and Definition of Terms</p> <ul style="list-style-type: none">Additional terms added. <p>Section 2 Introduction</p> <ul style="list-style-type: none">Minor clarifications on protocol versions for main (randomized) and sub-study. <p>Section 2.1 Changes from the Protocol:</p> <ul style="list-style-type: none">Described additional changes from protocol including use of log-rank test for time to first SSE; updated PFS-FAS analysis set; not re-testing final OS if interim OS is met and clarification of alpha levels if the interim OS analysis is not done. <p>Section 3 Study Design and Objectives:</p> <ul style="list-style-type: none">Minor formatting edits and clarifications on the dosimetry, pharmacokinetics and ECG sub-study in Germany. <p>Section 3.2 Randomization and Blinding:</p> <ul style="list-style-type: none">Minor edits and clarifications on sub-study enrollment. <p>Section 3.3 Study Objectives:</p> <ul style="list-style-type: none">Minor formatting edits. <p>Section 4 Planned Analyses:</p> <ul style="list-style-type: none">Clarified re-testing of final OS if interim OS is met and added alpha levels for final OS testing if interim OS analysis is not performed; added Section 4.2 for sub-study analyses.

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			<p>Section 4.1 Interim Analyses and IDMC Oversight</p> <ul style="list-style-type: none">Removed repeat text from sections 3.4 and 4. <p>Section 5 General Analysis Definitions:</p> <ul style="list-style-type: none">Clarified general analysis definitions including: definition of randomized treatment for main (randomized) and sub-study; definition of BSC/BSoC; definition of C1D1; start and end dates of NAAD as BSC/BSoC; date of last contact for overall survival; date of last administration and last exposure to randomized treatment; reference dates for safety and efficacy assessments; baseline definitions. <p>Section 5.1.2 Visit Windows:</p> <ul style="list-style-type: none">Clarified use of unscheduled assessments for PSA and HRQoL efficacy evaluations; removed listing of visit dates and flagging results not used in summary tables. <p>Section 5.2 Partial/Missing Dates:</p> <ul style="list-style-type: none">Clarified imputation rules and added rules for imputing date of last administration of BSC/BSoC, adverse event start dates and start of subsequent anti-cancer therapy. <p>Section 5.3 Definition of Populations:</p> <ul style="list-style-type: none">Minor clarification on analysis set definitions; removed PSMA-617 Safety Analysis Set; added Section 5.3.3 for sub-study populations. <p>Section 5.4 Subgroup Definitions:</p> <ul style="list-style-type: none">Minor clarifications on subgroup definitions including correcting age categories and adding multiple races to "other". <p>Section 5.4.1 Analyses on subgroups:</p> <ul style="list-style-type: none">Minor clarifications including clarification on key safety analyses to be performed. <p>Section 5.6 Variable Definitions:</p> <ul style="list-style-type: none">Clarified definition of duration of exposure and dose intensity; corrected month conversion factor for dose intensity; added definitions for: time to withdrawal of consent to randomized treatment and study, BMI, duration of exposure to BSC/BSoC, duration of exposure to NAAD as study BSC/BSoC, and stratification factors based on data collected on the eCRF. <p>Section 6.1 Patient Disposition:</p> <ul style="list-style-type: none">Removed reference to Appendix A (consort flow chart); clarified analyses for patient disposition

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			<p>including summarizing by subjects randomized prior to Mar 5, 2019 and on or after Mar 5, 2019; added Section 6.1.1 for sub-study analyses.</p> <p>Section 6.2 Protocol Deviations:</p> <ul style="list-style-type: none">Minor edits and clarifications; added analysis to describe and assess impact of COVID-19; added Section 6.2.1 for Sub-study specific analyses. <p>Section 6.3 Inclusion and Exclusion Criteria:</p> <ul style="list-style-type: none">Added summary tables for screened patients and for the PSMA-11 Safety Set and added Section 6.3.1 for sub-study specific analyses. <p>Section 6.4 Stratification Information:</p> <ul style="list-style-type: none">Minor clarifications including analysis set to use for listing; added an additional summary for the Response Evaluable Analysis Set. <p>Section 7 Baseline Characteristics and Prior and Concurrent Therapies and Medications</p> <ul style="list-style-type: none">Clarified analysis sets to use; added Section 7.5 for Sub-study specific analyses. <p>Section 7.1 Demographic and baseline assessments:</p> <ul style="list-style-type: none">Minor clarifications and additions including: added BMI; updated age categories; updated ECOG categories and clarified that ECOG was not collected at time of screening. <p>Section 7.2 Baseline Disease Characteristics:</p> <ul style="list-style-type: none">Minor clarifications including use of local assessments for site of disease and target/non-target lesion variables per RECIST 1.1. <p>Section 7.4 Prior Cancer Related Therapy:</p> <ul style="list-style-type: none">Removed summary of prior prostate cancer-related systemic therapy: last therapy; clarified coding dictionaries for prior surgeries and systemic therapies; clarified the variables to be summarized including: reason for prior surgery, prior number of NAAD-containing regimens, type of systemic therapy and last taxane therapy. <p>Section 8.1 Efficacy Variable Definitions:</p> <ul style="list-style-type: none">Moved text on radiographic imaging per local and central assessment from section 8.1.1 and provided more details on which independent reviewer from the central review is used for the analysis of rPFS, ORR, DCR, duration of response and PFS; clarified that radiographic imaging by local assessment will be used for a sensitivity analysis for rPFS only added Section 8.1.4 for Sub-study efficacy definitions.

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			<ul style="list-style-type: none">; added Section 8.1.4 for Sub-study efficacy definitions. <p>Section 8.1.1 Primary Efficacy Definitions:</p> <ul style="list-style-type: none">Clarified last contact date will be used for OS censoring; moved text on radiographic imaging per local and central assessment to Section 8.1; and minor updates to appendix references. <p>Section 8.1.2 Key Secondary Efficacy Definitions:</p> <ul style="list-style-type: none">Added best overall response category (Non-CR/Non-PD) for non-target lesions only. <p>Section 8.1.3 Additional Secondary Efficacy Definitions:</p> <ul style="list-style-type: none">Minor clarifications on baseline PSA definition, confirming PSA progression when no decline, confirming PSA response and use of scheduled and unscheduled assessments. <p>Section 8.2 Efficacy Analyses:</p> <ul style="list-style-type: none">Removed supportive analysis for ORR and DCR; clarified RECIST version; clarified that primary analysis of rPFS will be based on independent central review.Added Section 8.2.5 for sub-study specific efficacy analyses. <p>Section 8.2.1 Primary Efficacy Analyses:</p> <ul style="list-style-type: none">Minor formatting edits and clarifications including: re-testing of final OS if interim OS is met; cross reference to final OS analysis alpha levels when an interim OS analysis is not performed (Section 4); and rPFS will be based on independent central review. Added analyses for rPFS: based on local investigator, concordance between central and local review; modified analysis of missing and timing of tumor assessments; added descriptive analysis of OS using PFS-FAS; clarified median follow-up and 95% CI will be estimated using Kaplan-Meier method; added analyses to describe and adjust for impact of COVID-19 on rPFS and OS. <p>Section 8.2.2 Key Secondary Efficacy Analyses:</p> <ul style="list-style-type: none">Clarified rules for testing key secondary endpoints at final rPFS/interim OS and final OS including added confidence intervals; add rules for testing when the interim OS analysis is not performed; changed primary comparison method to stratified log-rank test for time to first SSE; clarified ORR, DCR and duration of response will be based on independent central review; removed additional analyses of ORR and DCR in PFS-FAS; corrected

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			<p>analysis set to use for duration of response; clarified mixture distribution analysis methodology.</p> <p>Section 8.2.3 Additional Secondary Efficacy Analyses:</p> <ul style="list-style-type: none">Clarified timing and analysis of secondary efficacy endpoints cross referencing back to the planned analyses section 4. <p>Section 8.2.3.1 Progression-free Survival Analysis:</p> <ul style="list-style-type: none">Clarified PFS will be based on independent central review; added the primary criteria of clinical progression to summary. <p>Section 8.2.3.2 Biochemical Response Analysis:</p> <ul style="list-style-type: none">Clarified that the 95% CI for the mean PSA doubling time will be presented; Corrected “maximum % decrease from baseline” to “maximum % change from baseline”; Added that differences in least square means and 95% confidence intervals will be presented for longitudinal models. <p>Section 8.2.3.3.1 EQ-5D-5L Questionnaire:</p> <ul style="list-style-type: none">Added plot for Utility Score; clarified clinical disease progression excludes radiographic and PSA progression; removed forest plots; added that differences in least square means and 95% confidence intervals will be presented for longitudinal models. <p>Section 8.2.3.3.2 FACT-P:</p> <ul style="list-style-type: none">Added plots for FACT-P Total score, FACT-G Total score, and TOI score; clarified clinical disease progression excludes radiographic and PSA progression; clarified the subscale analysis criteria for FACT-P total score; removed forest plots. <p>Section 8.2.3.3.3 BPI-SF:</p> <ul style="list-style-type: none">Added plots for Pain Intensity Scale, Pain Interference Scale and Worst Pain Intensity Scale; clarified clinical disease progression excludes radiographic and PSA progression; removed forest plots. <p>Section 8.2.3.3.4 Health Economics Analysis:</p> <ul style="list-style-type: none">Clarified that study specific analyses will focus on descriptive statistics of health resource utilization data. Removed all references to statistical analyses specifically hospitalizations, clinic visits and length of stay as these may be part of the economic evaluation performed by an external vendor. Clarified health utilization data definitions and summaries; removed monitoring activities as not required for health economic analysis; clarified

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			<p>that clinical disease progression excludes radiographic and PSA progression for time to first use of opioid analgesic.</p> <p>Section 9 Safety Evaluation:</p> <ul style="list-style-type: none">Clarified analysis sets to be used for the safety evaluation and how they will be presented in the summary tables. <p>Section 9.1 Extent of Exposure:</p> <ul style="list-style-type: none">Clarified analysis sets to be used for the exposure summaries; amended and clarified ^{177}Lu-PSMA-167 exposure summaries including overall exposure, dose interruptions, reductions and dose intensity; changed reference to "2018 Mar 1" WHO Drug Global dictionary version and replaced with general guidance that version will be presented as a footnote in tables and listings; added summary of exposure to NAAD as study BSoC; minor formatting edits for clarification and consistency throughout document; added Section 9.1.1 for sub-study specific analyses. <p>Section 9.2.2 General Convention:</p> <ul style="list-style-type: none">Clarified general conventions including when to assign treatment-emergent AEs as study drug-related when the assessment of relatedness is missing; clarified which AE summaries will include treatment emergent versus non-treatment emergent (i.e. AEs in LTFUP) and how summaries will be sorted. <p>Section 9.2.3 ^{68}Ga-PSMA-11 Adverse Events:</p> <ul style="list-style-type: none">Added summaries of serious and non-serious with occurrences AEs for clinical trial registry reporting; added analysis set to use for summaries; minor formatting edits; added Section 9.2.3.1 for sub-study specific analyses. <p>Section 9.2.4 Randomized Treatment Adverse Events:</p> <ul style="list-style-type: none">Added summaries of serious and non-serious with occurrences AEs for clinical trial registry reporting; clarified that TEAEs will be summarized by ^{177}Lu-PSMA-167 cycle of onset; minor edits/clarifications; added analysis set to use for summaries; clarified that non-treatment emergent AEs will be flagged; added analyses to describe and assess impact of COVID-19 on safety; added Section 9.2.4.1 for sub-study specific analyses. <p>Section 9.2.5 Deaths:</p> <ul style="list-style-type: none">Clarified summaries including which analysis set to use; added analyses to describe and assess impact

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			<p>of COVID-19 on safety; added Section 9.2.5.1 for sub-study specific analyses.</p> <p>Section 9.2.6 Long-term Follow up Adverse Events:</p> <ul style="list-style-type: none">Minor formatting edits; clarified analysis sets to use for summaries; added Grade 5 to summaries; clarified that AEs captured on LTFU CRF page are to be used in summaries and listed; added analyses to describe and assess impact of COVID-19 on safety; added Section 9.2.6.1 for sub-study specific analyses. <p>Section 9.2.7 Safety Topics of Interest:</p> <ul style="list-style-type: none">Added new section for summarizing safety topics of interest including Section 9.2.7.1 for sub-study specific analyses. <p>Section 9.3 Clinical Laboratory Determination:</p> <ul style="list-style-type: none">Minor formatting edits; minor clarifications on labs to summarize and list; clarified treatment period and analysis sets to use for summaries; added rules for imputing lab values reported with ">" or "<"; added shift tables for labs not graded per CTC using low/normal/high classification; added summary of liver function parameters; added Section 9.3.1 for sub-study specific analyses. <p>Section 9.4 Vital Signs, Physical Findings and ECG:</p> <ul style="list-style-type: none">Added clinically notable values for vital signs and ECGs; clarified treatment period for summaries; added ECOG PS change from baseline; removed derivation of QTcF using Fredericia's formula since uncorrected QT values is not collected; clarified that abnormal findings will be presented in listings and tables if appropriate; clarified analysis sets to use; added Section 9.4.1 for sub-study specific analyses. <p>Section 9.5 Prior and Concurrent Surgical and Therapeutic Procedures:</p> <ul style="list-style-type: none">Clarified treatment period and analysis set for summaries; removed text on summarizing active versus non-active procedures as not applicable; added Section 9.5.1 for sub-study specific analyses. <p>Section 9.6 Prior and Concurrent Radiotherapy:</p> <ul style="list-style-type: none">Added summaries for prior radiotherapy; clarified treatment period and analysis set for summaries; added Section 9.6.1 for sub-study specific analyses. <p>Section 9.7 Prior and Concomitant Medications:</p>

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			<ul style="list-style-type: none">Clarified treatment periods and analysis sets for summaries; added Section 9.7.1 for sub-study specific analyses. <p>Section 9.8 Post-Treatment Cancer-related Therapy:</p> <ul style="list-style-type: none">Changed reference to "2018 Mar 1" WHO Drug Global dictionary version and stated that version used will be reported in tables and listings; clarified that post-treatment therapy are therapies since discontinuation of randomized treatment; removed listing of long-term follow-up contact data; added Section 9.8.1 for sub-study specific analyses. <p>Appendices:</p> <ul style="list-style-type: none">Removed the example of the Consort Flow Diagram in Appendix A and renumbered appendices.