Clinical Development

lutetium (^{177}Lu) vipivotide tetraxetan

AAA617 ([^{177}Lu]Lu-PSMA-617)

2.5 Clinical Overview in prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer

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AAA	Advanced Accelerator Applications
AE	Adverse event
ALP	Alkaline phosphatase
APCCC	Advanced Prostate Cancer Consensus Conference
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AUCinf	Area under the curve extrapolated to infinity
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Products)
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSoC	Best standard of care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome
DCR	Disease control rate
DKFZ	Deutsches Krebsforschungszentrum (German Cancer Research Center)
DoR	Duration of response
DOTA	Dodecane tetraacetic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
FAS	Full Analysis Set
GBq	Gigabecquerel
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IV	Intravenous
LDH	Lactate dehydrogenase
MAA	Marketing Authorization Application
MATE1/MATE2	Multidrug and toxin extrusion protein 1/2
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical dictionary for regulatory activities

MRI	Magnetic resonance imaging
NAAD	Novel androgen axis drug (for example abiraterone or enzalutamide)
NCCN	Nation Comprehensive Cancer Network
NDA	New drug application
OAT1/OAT3	Organic anion transporter 1/3
OCT2	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PC	Prostate cancer
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PR	Partial response
PROs	Patient reported outcomes
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Radioligand therapy
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SD	Stable disease
SSE	Symptomatic skeletal event
TEAE	Treatment-emergent adverse event
USA	United States of America
WoC	Withdrawal of consent

1 Product development rationale

1.1 Background

Prostate cancer is globally the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths in 2020 worldwide (Sung et al 2021). It is the second leading cause of cancer-related death among men in the USA, and the third leading cause in Europe (Malvezzi et al 2019, Siegel et al 2020). In the USA, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020), and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths (International Agency for Research on Cancer 2020).

Treatment of PC is moving toward personalization using biomarkers and targeted therapy to optimize clinical outcomes, especially in high-risk and metastatic patients (Chakravarty et al 2018). Targeted RLT offers the possibility of treating the cancer lesions in a specific and tumor-selective manner by exploiting cell surface receptors mainly expressed on malignant cells. PSMA-targeted RLT utilizes radioisotopes such as Lu-177 complexed with a PSMA targeting moiety. After binding to the PSMA target, the radioligand is internalized into the PC cell to facilitate cell killing by release of beta particle radiation (Ghosh and Heston 2004, Benešová et al 2015), as discussed further in Section 1.1.1.

Despite the broadening therapeutic landscape for mCRPC over the last decade (as discussed in Section 6.1.2), there are limited options following progression on taxane-based chemotherapy, or when taxane-based chemotherapy is contraindicated in patients, or when patients are not candidates for taxane-based chemotherapy and do not have alternative options (Sartor et al 2018). These limitations underscore the necessity for improved treatment regimens with a significant antitumor effect and minimal toxicity.

1.1.1 Product and target indication

Prostate-specific membrane antigen

Prostate-specific membrane antigen is a type II transmembrane protein, also known as folate hydrolase I or glutamate carboxypeptidase II, and is a biological target for diagnostic imaging and therapy in PC (Silver et al 1997, O'Keefe et al 2018). PSMA is highly expressed in nearly all prostate cancers, including adenocarcinoma, but has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, renal proximal tubules, and salivary glands (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, androgen-independent prostate cancer (Wright et al 1995, Silver et al 1997, Bostwick et al 1998, Murphy et al 1998, Sweat et al 1998, Ross et al 2003, Chang 2004, Queisser et al 2015).

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA leads to internalization through endocytosis, and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003, Benešová et al 2015). This functional feature of PSMA allows for the development of low-molecular-

weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

^{177}Lu-PSMA-617

PSMA-617, the non-radioactive precursor molecule, consists of the PSMA-binding ligand glutamate-urea-lysine, a DOTA-chelator, and a linker connecting these 2 entities. This is then complexed with the lutetium radionuclide, and the radioactive nature of this metal is responsible for the therapeutic activity of ^{177}Lu-PSMA-617. The mechanism of action of ^{177}Lu-PSMA-617 is to deliver therapeutic radiation to prostate cancer cells via its binding to PSMA. By design, ^{177}Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015) that was further supported by published dosimetry studies (Delker et al 2016, Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017, Yadav et al 2017).

While PSMA-617 has the capacity to chelate other radionuclides, Lu-177 is the radionuclide of choice for this application, based on its favorable radiochemical characteristics, including half-life and the path length of the β-particles (Sgouros et al 2020). Lu-177 is a medium-energy β-emitter (497 keV) with a maximal tissue penetration of approximately 2 mm (mean=0.67 mm) and a physical half-life of 6.647 days (Deepa et al 2011, Dash et al 2015). The shorter β-range of Lu-177 provides better irradiation of small tumors, in contrast to the longer β-range of Y-90 (Emmett et al 2017). The shorter path length also acts to direct the energy within the tumor rather than into the surrounding normal tissues, while the path length is still sufficient to create bystander and crossfire effects within the tumor lesion. Lu-177 also has a relatively long physical half-life that, combined with the high intratumoral retention of ^{177}Lu-PSMA-617, reduces the dosing frequency. The retention half-life of the ^{177}Lu-PSMA-617 molecule in the tumor lesion has been reported to be between 60 and 160 hours, which is comparable to the 161-hour physical half-life of Lu-177 (Kratochwil et al 2019).

In this document, the therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan ([^{177}Lu]Lu-PSMA-617 / company research code: AAA617) is referred to as ^{177}Lu-PSMA-617, and the radiolabeled compound gallium (^{68}Ga) gozetotide ([^{68}Ga]Ga-PSMA-11 / company research code: AAA517) is referred to as ^{68}Ga-PSMA-11.

1.2 Clinical development program and influencing factors

1.2.1 Overview of the clinical development program

PSMA-617 was initially developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ), in collaboration with University Hospital Heidelberg (Kratochwil et al 2015). Following initial nonclinical development of PSMA-617, the compound was licensed to ABX GmbH in Germany.

Endocyte, Inc. assumed responsibility for global development of PSMA-617 in 2017, and initiated the pivotal Phase III Study PSMA-617-01 (also known as VISION). Another study, PSMA-617-02 (also known as RESIST-PC), was ongoing and since it was not consistent with the overall strategy of the company, Endocyte in agreement with the two principal investigators

decided to terminate enrollment prior to the planned enrollment of 200 patients. All patients who had been identified to Endocyte as potential study patients as of 22-Jun-2018 continued the screening process until 31-Jul-2018, and all patients previously enrolled continued to follow the protocol visit schedule through to completion of the study. Novartis acquired AAA in January 2018 and Endocyte, Inc. in December 2018.

The results from these two clinical studies (i.e., PSMA-617-01 and PSMA-617-02) form the basis for this application (Table 1-1). Data are not pooled due to the differences in the studies, considering their origins, designs (with and without comparator), target patient population, safety collection processes (e.g. AE severity grading), treatment regimen (with or without BSC/BSoC), and treatment duration.

Pivotal Study PSMA-617-01 (VISION) is an international, prospective, open-label, multicenter, randomized Phase III study of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC who were previously treated with 1-2 taxane-based chemotherapy regimens and at least 1 AR pathway inhibitor and who had a ^{68}Ga-PSMA-11 PET/CT scan that determined them eligible for inclusion. Patients were randomized in a 2:1 ratio to receive either 7.4 GBq (± 10%) ^{177}Lu-PSMA-617 plus BSC/BSoC or to receive BSC/BSoC only. A sub-study was also conducted in approximately 30 patients treated with ^{177}Lu-PSMA-617+BSC/BSoC at sites in Germany to evaluate radiation dosimetry, PK, ECGs, safety and tolerability, and urinary metabolic stability.

Supportive Study PSMA-617-02 (RESIST-PC) evaluated two doses of ^{177}Lu-PSMA-617 (6.0 GBq and 7.4 GBq) in a Phase II open-label, bicentric, randomized prospective setting. This study is only providing supportive safety data in this application, since only limited efficacy data were collected for this study following its termination (as described above).

Table 1-1 Overview of key prospective studies in the target indication

Study Status	Study design / Patient population	Key study endpoints	^{177}Lu-PSMA-617 Dose
Study PSMA-617-01 (VISION) Ongoing, closed to enrollment. Final analysis complete; DCO 27-Jan-2021	Phase III, multicenter, open-label, randomized study to evaluate the efficacy, safety, and tolerability of ^{177}Lu-PSMA-617+BSC/BSoC versus BSC/BSoC only / Male adult patients with progressive PSMA-positive mCRPC previously treated with 1 to 2 taxane-based chemotherapy regimens and at least one AR pathway inhibitor	*Primary*: rPFS and OS (alternate primary endpoints). *Key secondary*: ORR (CR+PR), DCR (CR+PR+SD) per RECIST v1.1, time to first SSE *Secondary*: DOR, PFS, biochemical response (PSA response, duration of PSA response, changes in PSA, ALP, LDH levels), safety, tolerability, HRQoL, and health economics.	Arm 1: ^{177}Lu-PSMA-617+ BSC/BSoC: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 i.v. every 6 weeks (±1 week) for a maximum of 6 cycles + BSC/BSoC as per physician's orders and protocol at the institution Arm 2: BSC/BSoC: BSC/BSoC as per physician's orders and protocol at the institution

Study Status	Study design / Patient population	Key study endpoints	^{177}Lu-PSMA-617 Dose
Study PSMA-617-01 Sub-study (VISION sub-study) Ongoing, closed to enrollment. Final analysis complete; DCO 27-Jan-2021	A dosimetry, PK, and ECG sub-study conducted in a non-randomized cohort of approximately 30 patients treated with ^{177}Lu-PSMA-617+BSC/BSoC at sites in Germany / Male adult patients with progressive PSMA-positive mCRPC previously treated with 1 to 2 taxane regimens and at least one AR pathway inhibitor	*Primary*: Whole body and organ radiation dosimetry of ^{177}Lu-PSMA-617 up to C1D8. *Secondary*: Pharmacokinetics, ECG, safety, tolerability, and metabolic stability of ^{177}Lu-PSMA-617 up to C1D8	Arm 1: ^{177}Lu-PSMA-617+BSC/BSoC: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 i.v. every 6 weeks (±1 week) for a maximum of 6 cycles + BSC/BSoC as per physician's discretion and protocol at the institution
Study PSMA-617-02 (RESIST-PC) Completed 08-Jan-2021 DCO 15-Jan-2020	Phase II, bicentric, open-label, randomized, study to evaluate the efficacy, safety and tolerability of ^{177}Lu-PSMA-617 / Male adult patients with progressive PSMA-positive mCRPC previously treated with ≥1 AR pathway inhibitor and either taxane-naive or taxane-treated	*Primary:* Clinical safety, 12-week PSA response[1], *Secondary*[1] Maximum PSA response, time to PSA progression, rPFS, DCR, QoL, pain scores, ECOG.	Group 1: 6.0 GBq (±10%) ^{177}Lu-PSMA-617 i.v. every 8 weeks (±1 week) until reaching 4 cycles or threshold maximum dose to the kidneys of 23 Gy as determined by dosimetry Group 2: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 i.v. every 8 weeks (±1 week) until reaching 4 cycles or threshold maximum dose to the kidneys of 23 Gy as determined by dosimetry

[1] Only data listings are available for selected efficacy endpoints.

All clinical studies included in this submission are listed in the [Tabular Listing of All Clinical Studies], and a summary of each study is provided in the [Synopses of Individual Studies].

All clinical studies were conducted in full compliance with current Good Clinical Practices. Study PSMA-617-01 was closely monitored by Endocyte/AAA personnel or a CRO for compliance to the protocol, SOPs, and applicable regulatory guidance, for the full length of the study. Study PSMA-617-02 was closely monitored by Endocyte personnel or a CRO, upon Endocyte acquiring IND 133661 for ^{177}Lu-PSMA-617 from Radiomedix.

1.2.2 Publications with efficacy and/or safety information for ^{177}Lu-PSMA-617

^{177}Lu-PSMA-617 has been used experimentally in the clinic since 2013 for the treatment of patients with mCRPC (Ahmadzadehfar et al 2015). The first published reports emerged in 2015, and many centers have since published on the efficacy and safety of ^{177}Lu-PSMA-617 in patients with mCRPC. Over 60 publications have summarized information from over 1900 subjects who were administered 1.1 to 12.0 GBq of ^{177}Lu-PSMA-617 every 4 to 12 weeks

for 1 to 9 cycles (Kulkarni et al 2018, Grubmüller et al 2019, Sarnelli et al 2019, Yadav et al 2020).

The 6 key published clinical studies providing evidence of the safety and efficacy of ^{177}Lu-PSMA-617 in a patient population similar to that in Study PSMA-617-01 (described in Section 4.3.1) are summarized in Table 1-2. A detailed summary of these relevant publications is presented in Section 8.

Table 1-2 Summary of published clinical studies on ^{177}Lu-PSMA-617 that included patients similar to those in Study PSMA-617-01

Source	Population	No. of patients	No. of PSMA-617-01-eligible patients	Dosing regimen	^{177}Lu-PSMA-617 dose	Efficacy endpoints
Prospective Phase II clinical studies						
Violet et al (2020)	Patients with PSMA-positive mCRPC who progressed after abiraterone acetate or enzalutamide and docetaxel or were not eligible for chemotherapy	50	39	1-4 cycles, every 6 weeks	Mean dose/cycle: 7.5 GBq (range: 4.0-8.9); mean total dose 24.7 GBq	≥ 50% PSA response (PCWG2); PSA PFS; RECIST v1.1 ORR (CR+PR); OS
Emmett et al (2019)	Patients with PSMA-positive mCRPC who progressed after abiraterone acetate or enzalutamide and docetaxel or were not eligible for chemotherapy	14	10	1-4 cycles, every 6 weeks	Mean dose/cycle: 7.0 GBq (range: 6.0-8.0)	≥ 50% PSA response (PCWG2); RECIST v1.1 ORR (CR+PR); OS
Hofman et al (2021)	Patients with PSMA-positive mCRPC suitable for cabazitaxel and previously treated with docetaxel with previous abiraterone acetate and/or enzalutamide permitted	200 (99 for ^{177}Lu-PSMA-617 arm; 101 for cabazitaxel arm)	91 ^{177}Lu-PSMA-617 arm	1-6 cycles, every 6 weeks	Planned: 8.5 GBq decreased by 0.5 GBq each cycle	≥ 50% PSA response (PCWG3); PSA PFS; RECIST v1.1 ORR (CR+PR); OS

Source	Population	No. of patients	No. of PSMA-617-01-eligible patients	Dosing regimen	^{177}Lu-PSMA-617 dose	Efficacy endpoints
Retrospective clinical studies						
Rahbar et al (2018)	Patients with PSMA-positive mCRPC who had been treated with at least one AR pathway inhibitor (abiraterone acetate and/or enzalutamide) as well as chemotherapy (docetaxel and/or cabazitaxel)	104	104	1-8 cycles, every 8 weeks	Median dose/cycle: 6.1 GBq (IQR: 5.9-6.3); median cumulative dose 18.8 GBq (IQR: 12.9-24.75)	≥ 50% PSA response (PCWG3); OS
van Kalmthout et al (2019)	Patients with PSMA-positive mCRPC previously treated with abiraterone acetate/ enzalutamide and/or chemotherapy (docetaxel/cabazitaxel) or were not eligible for chemotherapy	30	20	1-6 cycles, every 6 weeks; median of 6 weeks between cycles (range: 5.5-35)	Mean dose/cycle: 6 GBq (range: 5.6-6.4)	≥ 50% PSA response (PCWG3); PSMA PET imaging response; OS
Demirci et al (2017)	Patients with PSMA-positive mCRPC who progressed after abiraterone acetate or enzalutamide and docetaxel	43	42	1-4 cycles	Total dose (mean±SD): 21±7.2 GBq	> 50% PSA response1; PSA PFS; OS

Source: Demirci et al (2017), Rahbar et al (2018), Emmett et al (2019), van Kalmthout et al (2019), Violet et al (2020), Hofman et al (2021).

Baseline characteristics for all patients in these 6 key published clinical studies (3 prospective and 3 retrospective) are summarized in Table 1-3.

Table 1-3 Summary of baseline characteristics in patients treated with ^{177}Lu-PSMA-617 in published clinical studies that included patients similar to those in Study PSMA-617-01

	Violet et al 2020	Emmett et al 2019	Hofman et al 2021	Rahbar et al 2018	van Kalmthout et al 2019	Demirci et al 2017
n	50	14	99	104	30	43
Study type	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective
Age, median (years)	71 (min-max: 50-87)	69.5 (min-max: 56-81)	72 (IQR: 67-77)	70 (min-max: 64-76)	70 (min-max: 54-83)	Mean: 68.5 (min-max: 46-88)
# cycles	1-4 cycles, every 6 weeks	1-4 cycles, every 6 weeks	1-6 cycles, every 6 weeks	1-8 cycles, every 8 weeks	1-6 cycles	1-4 cycles
# cycles, median (range)	4 (1-4)	3 (2-4)	5 (IQR: 3-6)	3 (1-8)	4 (1-6)	4 (2-4)
^{177}Lu-PSMA-617 dose (GBq)	Mean 7.5 (range: 4.0-8.9)	Mean 7.0 (range: 6.0-8.0)	Planned: 8.5 Cycle 1, decrease 0.5 each cycle	Median 6.1 (IQR: 5.9-6.3)	Mean 6 (range: 5.6-6.4)	Cumulative dose 21+7.2
Site of metastases at study entry, n (%)						
Bone	38 (76%)	14 (100%)		101 (97%)	-	39 (90.7%)
Lymph node	2 (4%)	8 (57%)	-	80 (77%)	-	24 (55.8%)
Visceral	10 (20%)	4 (28%)	-	33 (32%)	-	8 (18.6%)
Prior treatment, n (%)						
PSMA-617-01-eligible	39 (78%)	10 (71%)	91 (92%)	104 (100%)	20 (67%)[1]	42 (98%)[1]
Docetaxel	42 (84%)	9 (64%)	99 (100%)	104 (100%)	-	-
Cabazitaxel	24 (48%)	6 (43%)	-	32 (31%)	-	-
Taxane-based chemotherapy	-	10 (71%)	-	-	20 (67%)	42 (98%)
Abiraterone	-	-	21 (21%)	83 (80%)	14 (47%)	-
Enzalutamide	-	-	49 (50%)	85 (82%)	22 (73%)	-

	Violet et al 2020	Emmett et al 2019	Hofman et al 2021	Rahbar et al 2018	van Kalmthout et al 2019	Demirci et al 2017
Abiraterone or enzalutamide or both	46 (92%)	-	-	-	-	-
Abiraterone or enzalutamide	-	14 (100%)	91 (92%)	104 (100%)	-	-
Abiraterone and enzalutamide	-	7 (50%)	21 (21%)	64 (61%)	-	-
ECOG						
0	20 (40%)	5 (36%)	42 (42%)	-	-	-
0-1	-	-	-	81 (78%)	-	-
1	22 (44%)	9 (64%)	53 (54%)	-	-	-
2	8 (16.0%)	-	4 (4%)	20 (19%)	-	-
3	-	-	-	3 (3%)	-	-
Unknown	-	-	-	-	-	-
PSA, ng/mL, median (min – max)	189.8 (7.0 – 4022.4)	88 (7-2950)	94 (IQR: 44 to 219)	361 (IQR: 80-755)	200 (4.3-3800)	264 (6-1187)
Alkaline phosphatase, U/L, median (min – max)	131 (49-1896)	-	111 (IQR: 83 to 199)	177 (IQR: 101-335)	-	-
LDH, U/L, median (min – max)	268 (148-1331)	-	-	283 (IQR: 221-416)	-	-

Source: Demirci et al (2017), Rahbar et al (2018), Emmett et al (2019), van Kalmthout et al (2019), Violet et al (2020), Hofman et al (2021)

A high-level summary of the efficacy results for all patients in the 6 key published clinical studies (3 prospective and 3 retrospective) is presented in Table 1-4.

Table 1-4 Summary of ^{177}Lu-PSMA-617 efficacy results from published clinical studies that included patients similar to those in Study PSMA-617-01

Study Number of patients	Median OS (months) (95% CI)	≥ 50% PSA response (%) (95% CI)	Median PFS (months) (95% CI)	ORR (CR+PR) (RECIST) (%)
Prospective Phase II clinical studies				
Violet et al (2020) N = 50	13.3 (10.5, 18.7)	64[5] (50, 77)	6.9[4] (6.0, 8.7)	56[2]
Emmett et al (2019) N = 14	11.5[1]	36[5]	NE	40[3]
Hofman et al (2021) N = 99 (^{177}Lu-PSMA-617 arm)	NE	66 (56, 75)	5.1 (3.4, 5.7)	49[10]
Retrospective clinical studies				
Rahbar et al (2018) N = 104	12.9 (11.6, 14.2)	33[6, 9]	NE	NE
van Kalmthout et al (2019) N = 30	11.3	57[6]	NE	NE
Demirci et al (2017) N = 43	15.9(13.1, 18.7)	53[7, 8]	6.5 (4-8.9)	NE

[1] Mean
[2] Based on 27 patients with measurable soft tissue disease (RECIST v1.1).
[3] Based on 10 patients with measurable soft tissue disease (RECIST v1.1).
[4] Defined by time to PSA progression as per PCWG2 criteria.
[5] Per PCWG2 criteria.
[6] Per PCWG3 criteria.
[7] >50% PSA response.
[8] PCWG criteria (2 or 3) not specified.
[9] Measured after the first cycle only prior to receiving further therapy cycles.
[10] Based on 37 patients with measurable soft tissue disease (RECIST v1.1).
NE = not evaluated.

Source: Demirci et al (2017), Rahbar et al (2018), Emmett et al (2019), van Kalmthout et al (2019), Violet et al (2020), Hofman et al (2021)

Overall, these published clinical studies support the use of ^{177}Lu-PSMA-617 in heavily pretreated patients with mCRPC, and are discussed in the context of the benefit/risk profile in Section 6.

1.2.3 Consideration of study design, guidelines, and regulatory input

1.2.3.1 Study PSMA-617-01 (VISION)

Study PSMA-617-01 is an international, prospective, open-label, multicenter, randomized Phase III study. Enrolled patients had a ^{68}Ga-PSMA-11 PET/CT scan assessed by a central reader, which determined them eligible for inclusion. Patients with progressive PSMA-positive mCRPC, who received at least one AR pathway inhibitor (as example enzalutamide or

abiraterone acetate) and were previously treated with 1 or 2 taxane-based chemotherapy regimens, were evaluated in this study. Patients treated with only 1 prior taxane-based chemotherapy regimen were eligible if the patient was unwilling to receive a second taxane regimen or the patient's physician deemed this unsuitable. Previous treatment options also included other chemotherapies or radiotherapy (such as ^{223}Ra dichloride).

The primary objective of this study utilized two alternate primary endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 plus BSC/BSoC compared with patients who received BSC/BSoC only. Randomization was in a 2:1 ratio to enable more patients to potentially benefit from ^{177}Lu-PSMA-617 treatment.

Key secondary endpoints were defined in line with PCWG3 as well as FDA and EMA guidance, and included ORR, DCR, and time to first SSE. The responses of soft tissue, lymph node, bone, and visceral lesions to treatment were characterized using RECIST v1.1 with the caveats outlined in the PCWG3 recommendations [Study PSMA-617-01-Appendix 16.1.1-Protocol-Appendix 7]. Many patients with mCRPC facing advanced illness with little hope for a cure have impaired physical, emotional, and functional well-being (Weinfurt et al 2005). Therefore, the study also evaluated changes in PRO assessments.

Radiologic tumor assessment followed the PCWG3 guidelines (Scher et al 2016) and included both CT with contrast/MRI imaging and bone scans with ^{99m}Tc-labeled diphosphonates. CT with contrast/MRI tumor assessments included evaluations of the chest, abdomen, and pelvis. A blinded independent central review (BICR) was conducted by two radiologists, and a third adjudicated discordant assessments. The on-site image review was used for patient management [Study PSMA-617-01-Appendix 16.1.1-Imaging Review Charter]. Radiographic imaging for tumor assessment was done every 8 weeks (± 4 days) after Cycle 1 Day 1 for the first 24 weeks (independent of dose delays), and every 12 weeks (± 4 days) thereafter.

Safety assessments made systematically during the study included monitoring of AEs and SAEs, blood chemistry, hematology and urine laboratory tests, and vital signs. Patients were also assessed by the investigator after 4 cycles for tolerance to treatment, evidence of response, and residual disease. Should the patients meet all criteria and agree to continue with additional treatment, then they proceeded to receive two additional cycles. All patients were observed closely for short- and long-term hematological and renal toxicity regardless of the number of cycles they received.

Best supportive/best standard of care (BSC/BSoC) for each patient was selected and optimized at the discretion of the patient's physician prior to randomization, and was administered as per the physician's discretion and protocol at the institution. BSC/BSoC therapy was broad but excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. Ra-223), or hemi-body radiotherapy treatments. The selection of BSC/BSoC was based on a number of factors recommended by healthcare practitioners experienced in the development of PC therapies, including:

1. Variability in global prescribing patterns and availability of different agents (to ensure the study could be international in scope)
2. The desire to provide good palliation and BSC/BSoC (since it is unethical to utilize a placebo in this population)

3. The concern that some investigators would not randomize patients to a control arm if access to an AR pathway inhibitor (as example enzalutamide or abiraterone acetate) was not allowed.

The options for BSC/BSoC fell into two broad categories: an AR pathway inhibitor for patients who were eligible, or palliative care. To provide a reliable estimate of the treatment effect for ^{177}Lu-PSMA-617, one of the randomization stratification factors at baseline was inclusion of an AR pathway inhibitor in BSC/BSoC at time of randomization (yes vs. no). In addition, none of the palliative care options included in the BSC/BSoC options have been shown to impact OS.

Early in the study, a high dropout rate among patients randomized to BSC/BSoC became evident. Overall, the actions taken to resolve this had no impact on either the interpretation or the robustness of the results from this study, as further discussed in Section 4.3.2.3.

Patients randomized to the treatment arm received BSC/BSoC and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles. The determination of the optimal dose and dose regimen was guided by efficacy and safety considerations, with an accounting for the life-threatening nature of the disease.

Within Study PSMA-617-01, a sub-study to evaluate dosimetry, PK, ECGs, safety and tolerability, and urinary metabolic stability was also conducted in a single-arm non-randomized cohort of approximately 30 patients. These patients received ^{177}Lu-PSMA-617+BSC/BSoC at sites in Germany, to provide a more complete assessment of these safety aspects of ^{177}Lu-PSMA-617. Patients in the sub-study were screened for eligibility, treated and followed-up similar to patients in the main study. These patients were not included in the analyses of the randomized part of the study.

Full details of the main study design are presented in [Study PSMA-617-01-Section 9]. Overall, the study design allowed the appropriate assessment of the efficacy and safety of ^{177}Lu-PSMA-617.

1.2.3.2 Study PSMA-617-02 (RESIST-PC)

Study PSMA-617-02 was a Phase II, bicentric, open-label, randomized, prospective study to evaluate the safety and efficacy of ^{177}Lu-PSMA-617. This study enrolled patients with progressive PSMA-positive mCRPC previously treated with ≥ 1 AR pathway inhibitor and who were either taxane-naive or taxane-pretreated. Enrolled patients had a ^{68}Ga-PSMA-11 PET/CT scan, which determined them eligible for inclusion, or a diagnostic ^{177}Lu-PSMA-617 scintigraphy or any equivalent PSMA-directed imaging, and were randomized to one of two treatment doses, one of which was similar to that administered in Study PSMA-617-01 (7.4 GBq) but given every 8 weeks (Table 1-1). Patients were able to receive BSC/BSoC during the study.

This study was ongoing when Endocyte acquired global development rights to PSMA-617, and was terminated early (enrollment ended as of 22-Jun-2018). All patients who were enrolled in Study PSMA-617-02 continued to follow the protocol visit schedule through to completion.

Full details of the study design are presented in [Study PSMA-617-02-Section 9].

1.2.3.3 Regulatory input

Key Health Authority interactions are summarized in Table 1-5.

Table 1-5 Key interactions with FDA and EMA

Interaction Date Sponsor	Objective	Outcome
FDA Type B End of Phase II Meeting under IND 133,661 30-Jan-2018 Endocyte, Inc.	To seek guidance on the proposed development of ^{177}Lu-PSMA-617 for mCRPC in patients expressing PSMA, who have already received abiraterone and/or enzalutamide and at least one prior taxane-containing regimen. The Sponsor's inquiry focused on the Phase III study, overall clinical and nonclinical plans for this therapeutic agent, as well as the proposed development plan of the radioactive diagnostic agent ^{68}Ga-PSMA-11, with intention to support registration.	Alignment on clinical and nonclinical development plans. The proposed nonclinical data package was acceptable to support NDA. Agreement on endpoints, comparators, safety monitoring by IDMC, eligibility criteria, dose and schedule, follow-up assessments.
FDA Type B End of Phase II Meeting under IND 133,661 16-Aug-2018 Endocyte, Inc.	To request feedback regarding the potential for an expedited path to submission based on data from Phase III Study PSMA-617-01. To seek feedback on using rPFS to support a NDA, assuming positive data from Study PSMA-617-01.	FDA stated that rPFS is an appropriate efficacy endpoint for regular approval, but that it should be assessed by independent central review and will depend on the magnitude of the effect and the risk-benefit compared to available therapies. The Sponsor should conduct a formal interim analysis of OS with α allocated at the time of the rPFS analysis. It will be important to demonstrate no detriment in OS at the time of this analysis.
BfArM Scientific Advice Meeting 13-Sep-2018 Endocyte, Inc.	To obtain scientific advice on the overall study design and other aspects of the clinical trial application of protocol version 1.0 (Study PSMA-617-01). The intent to amend the study and implement alternate (multiple) primary endpoints, rPFS and OS, as recently agreed with FDA.	BfArM stated that OS is an important endpoint which should be maintained. In addition, the Sponsor was strongly encouraged to seek centralized Scientific Advice regarding Study PSMA-617-01 and the overall development plans for marketing authorization from EMA.
FDA Type B CMC End of Phase II, written response only Meeting under IND 133,661 20-Dec-2018 Endocyte, Inc.	To discuss the proposed CMC development plan in support of a future NDA.	Alignment on the CMC development plan. The Agency agreed on the listed starting materials for the synthesis of the drug substance and drug product, (including two sources of $^{177}LuCl_3$), the proposed specifications for the drug substance and drug product and the proposed stability protocol.
EU Scientific Advice Working Party (SAWP)	To discuss the overall quality, nonclinical, and clinical	CHMP supported the overall proposed development plans.

Interaction Date Sponsor	Objective	Outcome
Procedure No.: EMEA/H/SA/4078/1/2019/III 10-Apr-2019 Endocyte, Inc.	development plans for ^{177}Lu-PSMA-617. As new information became available prior to the Scientific Advice meeting, operational, statistical, and design-related actions to mitigate an observed high withdrawal of consent (WoC) from the control arm were also shared and SAWP comments in this regard were included in the written advice.	CHMP considered the implementation of corrective actions to reduce the WoC in the control arm acceptable. CHMP highlighted that OS will be of paramount importance for benefit-risk assessment and to demonstrate efficacy in the setting of Study PSMA-617-01.
FDA Type A Meeting under IND 133,661 02-May-2019 Endocyte, Inc.	To obtain guidance on the operational, statistical, and design-related actions to mitigate the challenges caused by a high number of subjects withdrawing consent from the control arm of Study PSMA-617-01. To discuss the proposed approach to ensure a meaningful comparison between the randomized treatment arms for rPFS and OS.	FDA agreed to the operational plan to minimize the number of patients withdrawing consent from Study PSMA-617-01 trial and to closely monitor discontinuation. FDA considered the Sponsor's plans to increase enrollment and adjust the allocation of α between rPFS and OS to allow for analysis of fewer rPFS events acceptable.
BfArM Follow-up Scientific Advice 04-Feb-2020 Endocyte, Inc.	To review the changes made to the Study 617-PSMA-01 protocol v4.1	Alignment to proceed with resubmission of protocol v4.1
FDA Type C Meeting, written response only Meeting under IND 133,661 24-Mar-2020 Endocyte, Inc.	To obtain agreement on the overall organization and layout of the content that will be included in the NDA for ^{177}Lu-PSMA-617	FDA supported the organization and layout of the NDA content presented by the Sponsor, including Module 2 documents and the use of literature to support the application. FDA agreed with the planned analytical approach to bridge the clinical trial formulations of ^{177}Lu-PSMA-617 and the commercial formulation, the planned approach for process validation at the proposed manufacturing sites, and the proposed stability plan.
EMA Pre-submission Meeting 09-Jun-2020 Advanced Accelerator Applications	To obtain agreement on the overall organization and layout of the content that will be included in the MAA for ^{177}Lu-PSMA-617.	EMA provided an overall endorsement of all of the proposals related to the dossier and procedural aspects of the intended application, including helpful advice on which topics should be included in the context of (Co)-Rapporteur meetings.

Interaction Date Sponsor	Objective	Outcome
FDA Pre-NDA Meeting Meeting under IND 133,661 02-June-2021 Advanced Accelerator Applications	To obtain agreement on the clinical data package and overall content and structure of the planned NDA submission package for ^{177}Lu-PSMA-617.	FDA agreed with the overall content and structure of the NDA submission package (clinical data package, timing and contents of the safety update, analysis methods for endpoints). Agreement that an Assessment Aid will be provided. Sponsor will follow-up and provide further information on dosimetry/PK/ECG sub-study to the Agency to confirm the 505(b)(1) regulatory pathway.
Rapporteur/Co-Rapporteur Pre-submission Meeting 07-Jun-2021 Advanced Accelerator Applications	To obtain agreement on the clinical data package and overall content and structure of the planned MAA submission package for ^{177}Lu-PSMA-617.	The CHMP Rapporteur and Co-Rapporteur agreed with the overall content and structure of the MAA submission package. They agreed that data presented looked sufficient to support the assessment of [177Lu]Lu-PSMA-617 benefit-risk profile in the proposed indication.

Source: BfArM Initial Scientific Advice (2018), BfArM Follow-up Scientific Advice (2020), EMA Scientific Advice (2019), EMA Pre-submission (2020), EMA Pre-submission (2021), FDA EOP2 Type B (2018), FDA Type B (2018), FDA Type B CMC (2018), FDA Type A (2019), FDA Pre-NDA Type C (2020), FDA Pre-NDA (2021)

2 Overview of biopharmaceutics

^{177}Lu-PSMA-617 drug product is administered intravenously and the absolute bioavailability is 100%. Therefore, no dedicated biopharmaceutic studies for the ^{177}Lu-PSMA-617 drug product were conducted in humans, such as relative bioavailability, bioequivalence, or food effect [SBP-Section 4].

Different excipients [SBP-Section 1.2.4.1] were used in the clinical trial formulations of the ^{177}Lu-PSMA-617 drug product in Study PSMA-617-01 compared to the proposed commercial formulation. However, no impact is expected on the PK or biodistribution of ^{177}Lu-PSMA-617, and no bioequivalence studies were conducted, which is consistent with industry guidance for an intravenously administered drug product when differences in excipients are not expected to change the disposition of the active ingredient (EMA 2010, FDA 2019).

3 Overview of clinical pharmacology

Numerous publications in the literature summarize the evaluation of ^{177}Lu-PSMA-617 in mCRPC patients from populations with differing prior therapies and concomitant medications. These publications represent data from retrospective and prospective Phase 1, Phase 2 and dosimetry trials under country's local regulations using multiple sources of the PSMA-617 precursor and Lu-177 with different preparation processes for ^{177}Lu-PSMA-617. Despite these varying conditions, the literature suggests low toxicity and encouraging biochemical and radiographic response rates, overall survival and reduced pain using ^{177}Lu-PSMA-617 RLT in

patients with mCRPC (Rahbar et al 2017, Hofman et al 2018, Kim et al 2018, von Eyben et al 2018, Yadav et al 2019, Violet et al 2020, Hofman et al 2021, Sadaghiani et al 2021).

A sub-study within PSMA-617-01 evaluated dosimetry in 29 patients, and PK and ECG in 30 patients from a non-randomized cohort receiving ^{177}Lu-PSMA-617+BSC/BSoC. This section provides an overview of these sub-study results, with full details presented in the [SCP].

3.1 Pharmacokinetics of ^{177}Lu-PSMA-617

Based on the results of *in vitro* studies conducted either with unlabeled PSMA-617 or ^{175}Lu-PSMA-617 (or a mix), results are considered to be fully translatable to ^{177}Lu-PSMA-617 for the purpose of drawing pharmacokinetic conclusions.

3.1.1 Pharmacokinetic results from PSMA-617-01 sub-study

3.1.1.1 Blood-radioactivity single dose PK

Following an IV injection/infusion of ^{177}Lu-PSMA-617, time to peak whole blood concentrations (Tmax) ranged from 0.0167 to 1.68 hours, generally occurring within approximately 20 minutes after administration, with median Tmax value of 0.375 hours. Afterwards, whole blood concentrations declined with a geometric mean terminal elimination half-life of approximately 41.6 (geometric mean %CV 68.8%) hours. The geometric mean total systemic clearance (CL) was 2.04 L/hr (31.5%) in line with CL estimated by a population PK approach. Given the determined protein binding and information about excretion (and lack of transporter interaction), total clearance can be assumed to be equal to passive renal clearance. Geometric mean apparent volume of distribution (Vz) was 123 L (78.1%). The effective half-live, accounting for both the physical half-life (radioactive decay of the Lu-177 radionuclide) and the terminal elimination half-life (41.6 hours for ^{177}Lu-PSMA-617), is calculated to be ~33 hours [SCP–Section 3.1.1].

3.1.1.2 Absorption, distribution, metabolism, excretion

As ^{177}Lu-PSMA-617 is administered intravenously, bioavailability is 100%. ^{177}Lu-PSMA-617 displays moderate protein binding with a fraction bound of ~60-70% and does not distribute to erythrocytes. ^{177}Lu-PSMA-617 is metabolically stable both in vitro and in vivo and primarily excreted passively via the kidney [SCP–Section 1.2.1.2].

3.1.1.3 Effects of intrinsic factors on PK and dosimetry

Demographic factors

The PK and dosimetry of ^{177}Lu-PSMA-617 has been limited to investigations in prostate cancer, exclusive to males, therefore there is no information regarding the impact of gender on PK or biodistribution. Population PK and dosimetry analyses showed that ^{177}Lu-PSMA-617 exposure and biodistribution are not affected by body weight, supporting the use of fixed dosing. No information is currently available about the effects of ethnicity or race on biodistribution and PK of ^{177}Lu-PSMA-617. Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors. Age in the range of 52 to 80 years (median 67 years) was shown not to have an effect on the

exposure of ^{177}Lu-PSMA-617 in the PSMA-617-01 sub-study. While older subjects were associated with higher radiation absorbed dose levels in the kidneys and bone marrow, this correlation may be confounded by the negative correlation between age and renal clearance [SCP-Section 3.3.3].

Hepatic impairment

As ^{177}Lu-PSMA-617 is not metabolized by, or primarily eliminated through, the liver, PK and biodistribution are not affected by hepatic impairment [SCP-Section 3.4.8]. Hence, no dose adjustment is needed in patients with hepatic impairment.

Renal impairment

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted. Based on popPK and dosimetry correlation analysis [SCP-Section 3.3.2] between PK and dosimetry and renal function, mild or moderate renal impairment does not warrant any dose adjustments. The pharmacokinetic profile and safety of ^{177}Lu-PSMA-617 have not been studied in patients with severe renal impairment (CLcr 15 to 29 ml/min) or end-stage renal disease, therefore no information is available in such patients.

3.1.1.4 Effects of extrinsic factors on PK and dosimetry

Co-administration with other medications

As ^{177}Lu-PSMA-617 is metabolically stable both in vitro and in vivo, passively cleared via the kidney and not a substrate of any of the investigated uptake or efflux transporters (MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp, and BCRP) based on in vitro assessments using a test formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions in vivo.

Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to regulate PSMA expression in some nonclinical prostate cancer models, and in some clinical studies. However, a definitive effect of these therapies on the PK or biodistribution of ^{177}Lu-PSMA-617, particularly in normal tissues, has not been established. Additionally, the dosimetry results acquired from patients in the PSMA-617-01 sub-study, which allowed concomitant administration of AR pathway inhibitors, showed good concordance with literature. Considering the general consistency in the reported biodistribution, ADTs appear unlikely to have an effect on the biodistribution and PK of ^{177}Lu-PSMA-617 that extends beyond the normal range of variability. Co-administration of ADT or other androgen pathway targeting therapies does not warrant dose adjustments of ^{177}Lu-PSMA-617 as supported by the safety profile and efficacy of ^{177}Lu-PSMA-617 in PSMA-617-01 [SCP-Section 3.5.1].

3.1.1.5 Effect of ^{177}Lu-PSMA-617 on concomitant medications

Based on the risk assessment on in vitro data described in [SCP-Section 3.5.2] using a test formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, ^{177}Lu-PSMA-617 does not induce CYP1A2, 2B6 or 3A4 and does not inhibit all common CYPs (CYP1A2, 2B6, 2C8, 2C9,

2C19, 2D6, 3A4/5) and investigated efflux and uptake transporters (BCRP, BSEP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2).

Therefore, ^{177}Lu-PSMA-617 is not expected to cause any CYP- or transporter-mediated drug interactions in vivo.

3.1.2 Dosimetry results from PSMA-617-01 sub-study

Radiation exposures from the PSMA-617-01 sub-study, especially for the organs considered at risk from radiation due to their exposure levels such as salivary glands, lacrimal glands, kidneys and bone marrow, were consistent with the ranges published in literature. Overall, the dosimetry data indicates minimal risk for patients based on the theoretical calculated radiation exposure after 6 cycles of 7.4 GBq. The sub-study dosimetry data is in line with clinical findings from the PSMA-617-01 main study that indicate AEs related with these organs are generally of a low-to-moderate severity, tolerable and of a reversible nature (Section 5). Comparison with literature values and with the observed safety profile in the PSMA-617-01 main study per organ at risk are discussed in more detail in [SCP-Section 3.3.2].

3.2 Pharmacodynamics

No relevant pharmacodynamic (PD) effects related to the unlabeled PSMA-617 precursor molecule itself are expected, as the mass dose is very low (a potential maximum of 275 µg), it is administered infrequently, and nonclinical studies demonstrated a lack of direct pharmacological or toxicological effects across *in vitro* and *in vivo* assays at much higher exposures [SCP-Section 3.6].

3.3 Exposure-Response

3.3.1.1 PK/QT analysis

The results of the PK/QT analysis, together with the preclinical cardiac safety studies, indicating a negligible risk of an electrophysiological effect by ^{175}Lu-PSMA-617, low radiation uptake in the heart, and the absence of clinical findings related to QT prolongation in the PSMA-617-01 sub-study, confirm that ^{177}Lu-PSMA-617 administration does not pose a cardiac risk. These results are further presented in [SCP-Section 3.7.1], and are confirmed by clinical safety data from PSMA-617-01 showing that ^{177}Lu-PSMA-617 had no effects on heart rate, PR interval, QRS duration, or QTcF (Section 5.2.2.7).

3.3.1.2 Exposure-dosimetry

^{177}Lu-PSMA-617 PK exposure effect on dosimetry for the organs at risk (i.e. kidney, bone marrow, salivary and lacrimal glands) during the first cycle of treatment in sub-study patients of PSMA-617-01 were explored [SCP-Section 3.7.3]. A linear regression was performed for each exposure-dosimetry relationship, and showed that only AUCinf in blood was a statistically significant predictor of the radiation absorbed dose in the kidneys (p=0.005). AUCinf is largely influenced by creatinine clearance, a marker of renal clearance, as shown by the population PK model that identified baseline creatinine clearance ($CLcr_{BL}$) as a significant covariate in the population PK model with a strong effect on exposure. However, the relationship between AUCinf and kidney dosimetry may not be a causal relationship as it is confounded by CLcr.

Indeed, CLcr has a strong effect on AUCinf, and is also highly negatively correlated with kidney dosimetry.

3.3.1.3 Exposure/dosimetry-acute toxicity

Effects of exposure and organ dosimetry on acute toxicity at Cycle 1 related to the organs at risk (i.e. kidney, bone marrow, salivary and lacrimal glands) were explored in the sub-study of PSMA-617-01 [SCP-Section 3.7.2]. While exposure/dosimetry-acute toxicity analyses were limited by the small sample size and the small number of adverse events (and explored only Cycle 1 at present stage), higher injected activity and higher kidney radiation absorbed dose tend to be associated with larger decrease from baseline in CLcr. No trend was detected between hematological adverse events of CTCAE grade ≥ 2 and salivary gland toxicities with exposure metrics measured at cycle 1.

4 Overview of efficacy

This section discusses the efficacy of ^{177}Lu-PSMA-617 observed in the pivotal Phase III Study PSMA-617-01. Study PSMA-617-02 is not presented since only limited efficacy data were collected for this study following its termination. A full systematic review of the Study PSMA-617-01 efficacy results is provided in the [SCE].

Study PSMA-617-01 demonstrated that adding ^{177}Lu-PSMA-617 to BSC/BSoC produced a statistically significant improvement in rPFS and OS and in all key secondary endpoints. As discussed in Section 6.2, these results show that ^{177}Lu-PSMA-617 is a new, more effective treatment option for patients with PSMA-positive mCRPC.

4.1 Dose-selection rationale

The recommended treatment regimen for ^{177}Lu-PSMA-617 comprises a total of 6 cycles (doses) of 7.4 GBq administered intravenously every 6 weeks (± 1 week). The rationale for this is fully described in [SCE-Section-4.2], and this section summarizes key information.

The selection of the ^{177}Lu-PSMA-617 7.4 GBq dose for Study PSMA-617-01 was determined by considering prior clinical experience regarding efficacy and safety, dosimetric evaluation and radiosensitivity, and RLT class-based information from Lutathera [SCP-Section 3.3.1]. Lutathera was the first approved peptide-based ^{177}Lu-radioligand therapeutic, and utilizes a dose of 7.4 GBq every 8 weeks for a total of 4 cycles, although other doses and schedules have been evaluated in the literature. The published experience with Lutathera informed much of the early development work that has been done with ^{177}Lu-PSMA-617. Considering Lutathera as a comparator is particularly relevant, as the kidney dosimetry profile for both agents is similar, due to the renal clearance of both agents, as well as their target expression on the renal proximal tubules. Based on the extensive clinical experience with Lutathera, the kidney absorbed radiation dose thresholds in RLT were suggested to be higher than the EBRT threshold for kidneys suggested by several authors (Wessels et al 2008, Bergsma et al 2016). For further details, see [SCP-Section 3.3.1.3].

Recent publications show that cumulative doses of 30 to 60 GBq of ^{177}Lu-PSMA-617 may be possible without adverse effects on renal tissue (Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017), 45 to 73.8 GBq for hematological tissue (Kabasakal et al 2017, Scarpa et al

2017), and 50 GBq for salivary glands (Virgolini et al 2018). The majority of the publications used a regimen of 4 cycles of 6 GBq every 8 weeks. However, efficacy and safety information from the prospective Phase II study by Hofman et al (2018) suggested that dosing of 4.4 to 8.7 GBq (mean: 7.5) every 6 weeks for 4 cycles was well tolerated and efficacious. Other clinical publications show that more than 4 cycles of ^{177}Lu-PSMA-617 can safely be administered as a means to maximize the benefit to the patient (Rahbar et al 2018), as discussed in [SCE-Section-4.2].

Based on these published data, and with the purpose of delivering the highest possible dose to the tumor to maximize the chance for an effective antitumor effect without causing serious toxicity in the patient, a dose of 7.4 GBq ^{177}Lu-PSMA-617 administered intravenously once every 6 weeks for a maximum of 6 cycles was selected for Study PSMA-617-01, for a maximum cumulative dose of 44.4 GBq.

In Study PSMA-617-01, the dose was to be administered slowly by intravenous route, with a saline flush both before and after administration of the dose. The actual method of administration selected to deliver the dose intravenously to the patient was recorded in the CRF. Syringe with or without a pump was the predominant method selected for administration of ^{177}Lu-PSMA-617 in PSMA-617-01 with 1784 total administrations. The other 2 intravenous methods of administration, gravity method and vial with pump, were selected much less frequently in PSMA-617-01 with 229 and 344 total administrations, respectively. These data support the inclusion of 3 intravenous methods considered appropriate and safe for administration of the commercial drug product: intravenous injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump), or intravenous infusion using either the gravity method (with or without an infusion pump) or using the vial (with a peristaltic infusion pump). Instructions for each of these intravenous methods of administration are proposed in the labeling based on experience in PSMA-617-01 and on class-based experience with other RLTs such as Lutathera. For further details, see [SCP-Section 3.3.1.3].

Efficacy and safety results from Study PSMA-617-01 support the proposed dose and regimen (Section 4 and Section 5), and additional evidence for using a total of 6 cycles in patients is also provided by the following sub-group analyses from Study PSMA-617-01 in the 69 patients who received 4 cycles, and the 289 patients who received 5-6 cycles (FAS Safety set):

- Median **rPFS** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 6.4 months (95% CI: 4.3, 7.9); for patients who received 5-6 cycles, median rPFS was 13.8 months (95% CI: 12.2, 17.0) [SCE Appendix 1-Table 14.2.2.20].
- Median **OS** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 11.0 months (95% CI: 9.6, 12.6); for patients who received 5-6 cycles, median OS was 24.7 months (95% CI: 21.3, 27.6) [SCE Appendix 1-Table 14.2.1.12].
- Median **PFS** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.4 months (95% CI: 3.3, 4.7); for patients who received 5-6 cycles, median PFS was 9.9 months (95% CI: 8.6, 11.3) [SCE Appendix 1-Table 14.2.5.1].
- Median **time to worsening in FACT-P** total score for patients who received 4 cycles of 177Lu-PSMA-617 was 5.4 months (95% CI: 4.2, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-P total score was 9.2 months (95% CI: 8.3, 11.1) [SCE Appendix 1-Table 14.2.8.1.2.2].

- Median **time to worsening in FACT-G** total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.6, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-G total score was 10.3 months (95% CI: 8.8, 11.4) [SCE Appendix 1-Table 14.2.8.10.2.2].
- Median **time to worsening in BPI-SF pain intensity** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.7 months (95% CI: 3.1, 5.7); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain intensity was 9.4 months (95% CI: 8.5, 10.8) [SCE Appendix 1-Table 14.2.9.1.2.2].
- Median **time to worsening in BPI-SF pain interference** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.4, 6.0); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain interference was 8.8 months (95% CI: 7.4, 10.4) [SCE Appendix 1-Table 14.2.9.2.2.2].
- As discussed in [SCS-Section 5.2.3.1], AEs were also assessed in patients who received ≤4 cycles of ^{177}Lu-PSMA-617 and in those who received 5 or 6 cycles. Overall, there was no suggestion of a safety concern in patients who received more cycles.

Overall, the safety and efficacy results of Study PSMA-617-01, and the dosimetry results from the sub-study, provide a robust assessment of the proposed dose and the dosing schedule, and support a recommended dosage of 7.4 GBq (200 mCi) every 6 weeks (± 1 week) for a total of 6 cycles of ^{177}Lu-PSMA-617.

4.2 Efficacy criteria and efficacy evaluation

The design of Study PSMA-617-01 is summarized in Section 1.2.1 and described in detail in [Study PSMA-617-01-Section 9].

Alternate primary endpoints were utilized, which are considered multiple primary endpoints as discussed in the ICH E9 Guideline "Statistical Principles for Clinical Trials" (EMA 1998), the FDA Guidance "Multiple Endpoints in Clinical Trials" (FDA 2017), as well as the EMA "Guideline on multiplicity issues in clinical trials" (EMA 2017). The statistical design of the study was such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated α level. When using alternate primary endpoints, although demonstration of a treatment effect on at least one of the 2 alternate primary endpoints is sufficient, results for all of the pre-specified alternate primary endpoints (rPFS and OS in this case), both positive and negative, are considered in the overall assessment of risks and benefits [Study PSMA-617-01-Appendix 16.1.9].

Progression-free survival in mCRPC trials has been inconsistently defined and poorly associated with OS. For this reason, rPFS was chosen as an alternate primary endpoint as it is a robust endpoint associated with OS, and is recommended by PCWG3 guidelines (Morris et al 2015, Scher et al 2016, Rathkopf et al 2018). The alternate primary endpoints of rPFS and OS were previously used in other mCRPC clinical trials (Ryan et al 2013, Beer et al 2014).

The sample size in Study PSMA-617-01 was determined based on the alternate primary endpoints of rPFS and OS. 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 was expected to yield 508 deaths. This number of events provided at least 90% power to test the hypothesis that the HR for OS is 0.7306 or better with a 1-sided α level of at least 0.020. These

final OS data were analyzed with a 1-sided α level depending on the final rPFS results [Study PSMA-617-01-Section 9.8.3].

For rPFS, a total of approximately 557/814 patients were expected to be randomized on or after 05-Mar-2019 (after enhanced study site education measures were implemented) for the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients were expected to yield 364 rPFS events which was sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 0.67 or better with a 1-sided α level of 0.004. Blinded independent central review assessments were used to determine rPFS events.

The α level applicable to the analysis of the key secondary endpoints ORR, DCR, and time to SSE depended on the statistically significant results of the final OS analysis based on the Hochberg closed test procedure [SCE-Table 1-3], [Study PSMA-617-01-Section 9.7.6]. The way the α was allocated in the testing strategy is displayed in [SCE-Table 8.1].

A full description of statistical methodology employed in Study PSMA-617-01 is provided in [Study PSMA-617-01-Appendix 16.1.9].

4.3 Efficacy results

4.3.1 Study population in Study PSMA-617-01

The population of patients reflects the target population for whom the drug is intended, namely heavily pretreated patients with progressive PSMA-positive mCRPC, as further described in [Study PSMA-617-01-Section 10.4].

Overall, a total of 831 patients were randomized and included in the FAS population; 75.3% of whom were ≥ 65 years and 92.4% had an ECOG PS score of 0-1. The median time since initial diagnosis was 7.4 years (range: 0.7, 28.9), almost all (96.3%) had at least one PC-related surgery (including biopsies), and 43.2% had received therapeutic surgery. The majority of patients (76.1%) also had at least one PC-related radiotherapy, and 79.1% had received more than 3 different regimens of prior systemic therapy. All patients had received prior taxane treatment and a prior AR pathway inhibitor [Study PSMA-617-01-Section 10.4.2].

The FAS population (N=831) included all patients randomized to either ^{177}Lu-PSMA-617+BSC/BSoC or BSC/BSoC only, and was used to analyze OS. The PFS-FAS population (N=581, sample size discussed in [Study PSMA-617-01-Section 9.8]) included all patients randomized on or after 05-Mar-2019 (after enhanced study site education measures were implemented), and was used to analyze rPFS and all other secondary endpoints, except for ORR and DCR. These 2 endpoints were analyzed with the Response evaluable analysis set (N=439), which comprised a subset of patients from the PFS-FAS population with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per blinded independent central review) [Study PSMA-617-01-Section 10.3].

There was a low representation of patients who were Black or African American (6.6% of patients overall) or Asian (2.4%). However, this was balanced between the two treatment arms.

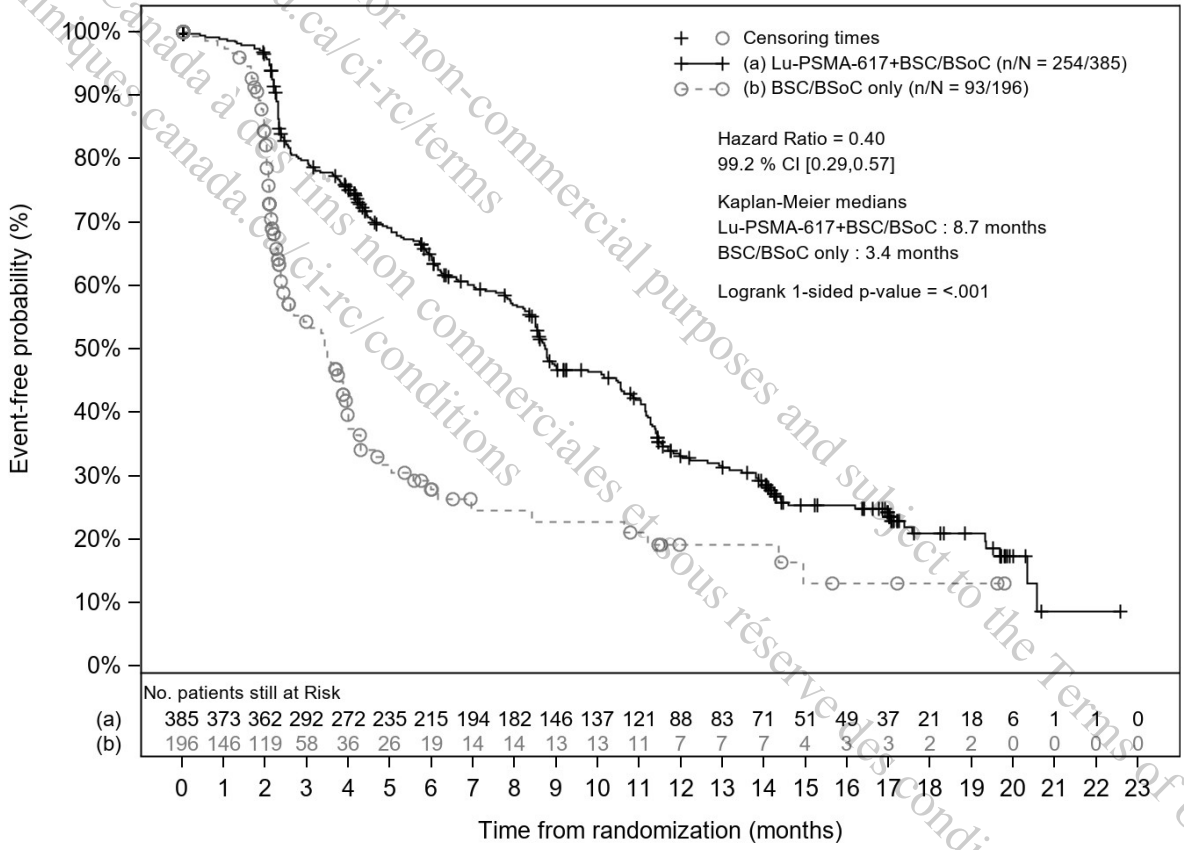
Demographic and baseline disease characteristics (including prognostic factors) were well balanced between the two treatment arms, providing reassurance as to the interpretation of treatment comparisons.

4.3.2 Alternate primary endpoints and supportive analyses from Study PSMA-617-01

4.3.2.1 rPFS

For the alternate primary endpoint of rPFS based on BICR per PCWG3 criteria, an estimated 60% reduction in the risk of radiographic disease progression or death was observed in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (Figure 4-1). This was statistically significant, with a one-sided stratified log-rank test of $p < 0.001$.

Figure 4-1 Study PSMA-617-01: Kaplan-Meier plot of rPFS based on blinded independent central review (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.2.1]

The HR was 0.40 (99.2% CI: 0.29, 0.57) in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only, with a median rPFS of 8.7 months (99.2% CI: 7.9, 10.8) and 3.4 months (99.2% CI: 2.4, 4.0), respectively (Table 4-1). Thus, the median rPFS was prolonged by 5.3 months.

Table 4-1 Study PSMA-617-01: rPFS based on a blinded independent central review using stratified log-rank test and Cox regression model (PFS-FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=385	BSC/BSoC only N=196
rPFS, n (%)		
Events (progression or death)	254 (66.0)	93 (47.4)
Radiographic progressions	171 (44.4)	59 (30.1)
Deaths	83 (21.6)	34 (17.3)
Censored	131 (34.0)	103 (52.6)
Ongoing without event	90 (23.4)	24 (12.2)
Event documented after 2 or more missed tumor assessments	36 (9.4)	44 (22.4)
Adequate assessment not available[1]	5 (1.3)	35 (17.9)
Kaplan-Meier estimates (months)		
25th percentile [99.2% CI]	4.1 [2.6, 4.9]	2.1 [2.0, 2.3]
Median rPFS [99.2% CI]	8.7 [7.9, 10.8]	3.4 [2.4, 4.0]
75th percentile [99.2% CI]	16.2 [12.9, NE]	7.0 [4.2, NE]
rPFS rates (%)		
3 months (SE) [99.2% CI]	79.8 (2.09) [73.6, 84.7]	54.3 (4.41) [42.0, 65.1]
6 months (SE) [99.2% CI]	64.6 (2.53) [57.5, 70.9]	27.8 (4.51) [16.7, 40.1]
12 months (SE) [99.2% CI]	33.2 (2.67) [26.2, 40.3]	19.1 (4.50) [9.0, 32.1]
HR (stratified Cox PH model)	0.40	
99.2% CI[2, 3]	[0.29, 0.57]	
Stratified Log-rank Test one-sided p-value[3]	< 0.001	
Follow-up time (months)[4]		
Median [95% CI]	16.4 [14.3, 17.0]	3.9 [2.4, 5.4]
Minimum-Maximum	0.0 - 22.6	0.0 - 19.8

[1] Patients censored without adequate post-baseline evaluations or adequate baseline assessment.

[2] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.

[3] Both Cox PH model and Log-rank test are stratified for 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 BSC/BSoC at time of randomization (yes vs. no). IRT data for stratification are used.

[4] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for death or radiographic progression.

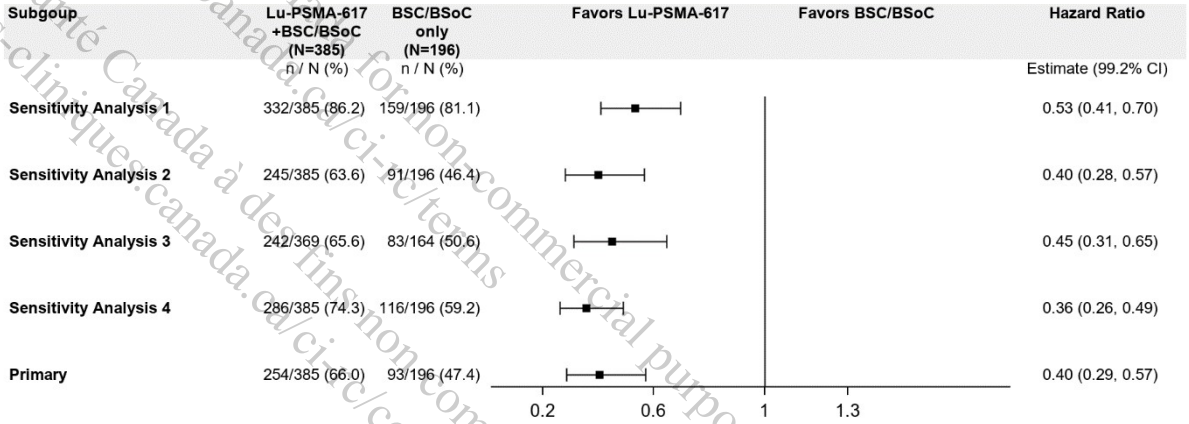
Source: [Study PSMA-617-01-Table 14.2.2.1]

Results of multiple preplanned sensitivity analyses demonstrated that the observed benefit in rPFS was robust, with estimated HRs ranging from 0.36 to 0.53 (Figure 4-2). Further details are presented in [Study PSMA-617-01-Section 11.1.3.1]:

- Sensitivity analysis 1:
  - Includes events regardless of intervening missed assessments
  - Bone PDs were indicated per PCWG3 guidelines with modified rules for confirmation after week 16
  - Included all radiographic PD and deaths captured in the study, including scans not centrally read that were captured on the LTFU CRF page

- Sensitivity analysis 2: deaths occurring after start of a new anticancer therapy were censored at start date of the new therapy.
- Sensitivity analysis 3: rPFS was defined from the date of first dose of randomized treatment.
- Sensitivity analysis 4: local investigator assessments were used instead of central reading.

Figure 4-2 Study PSMA-617-01: rPFS treatment effect sensitivity analyses per blinded independent central review - Forest plot of HR with 99.2% CI (PFS-FAS)



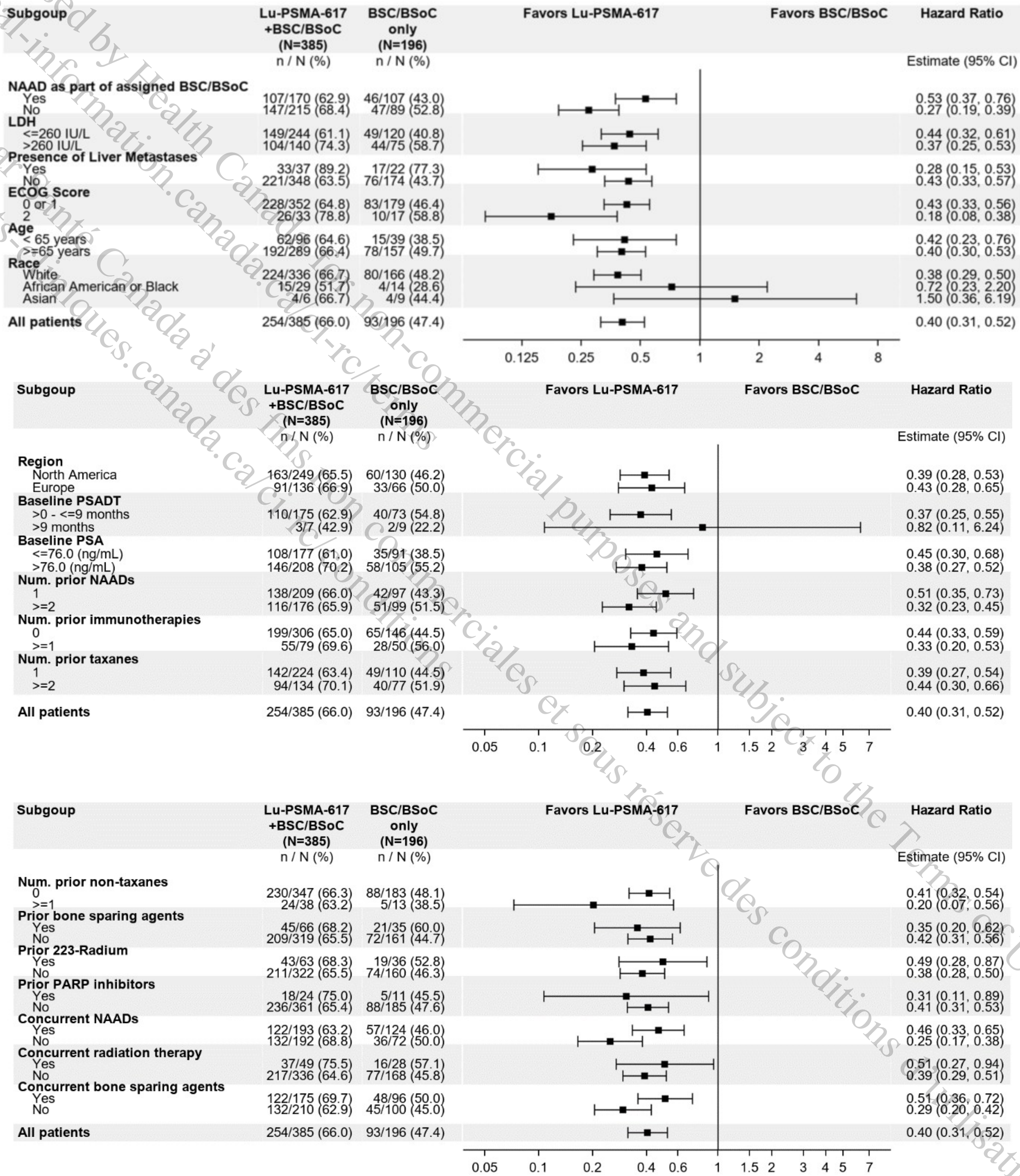
n/N: number of events/number of patients in treatment arm.
Vertical line shows the no effect point.
Source: [Study PSMA-617-01-Figure 14.2.2.3]

In addition, further analyses on rPFS were performed:

- The robustness of the primary analysis was further confirmed by an analysis of rPFS conducted based on the FAS [SCE-Section-3.2.1.1.1].
- Sensitivity analyses assessed the impact of COVID-19 on rPFS. Results were also similar to those for the primary analysis [Study PSMA-617-01-Table 14.2.2.17], [Study PSMA-617-01-Table 14.2.2.18].
- A panel of analyses were also performed to assess the sensitivity of rPFS to censoring due to drop-outs. These were also consistent with the primary analysis of rPFS, and are discussed in Section 4.3.2.3 and presented in detail in [SCE-Table 3-15].

Subgroup analyses of rPFS were consistent with the primary rPFS analysis and demonstrated homogeneity of the treatment effect across these subgroups (Figure 4-3), with the exception of subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and PSADT >9 months subgroups). Further details on these analyses are presented in [SCE-Section 3.3].

Figure 4-3 Study PSMA-617-01: rPFS treatment effect for patient subgroups per blinded independent central review - Forest plot of HR with 95% CI (PFS-FAS)


Subgoup | Lu-PSMA-617 +BSC/BSoC (N=385) n / N (%) | BSC/BSoC only (N=196) n / N (%) | Favors Lu-PSMA-617 | Favors BSC/BSoC | Hazard Ratio Estimate (95% CI)
NAAD as part of assigned BSC/BSoC
Yes 107/170 (62.9) 46/107 (43.0) 0.53 (0.37, 0.76)
No 147/215 (68.4) 47/89 (52.8) 0.27 (0.19, 0.39)
LDH
<=260 IU/L 149/244 (61.1) 49/120 (40.8) 0.44 (0.32, 0.61)
>260 IU/L 104/140 (74.3) 44/75 (58.7) 0.37 (0.25, 0.53)
Presence of Liver Metastases
Yes 33/37 (89.2) 17/22 (77.3) 0.28 (0.15, 0.53)
No 221/348 (63.5) 76/174 (43.7) 0.43 (0.33, 0.57)
ECOG Score
0 or 1 228/352 (64.8) 83/179 (46.4) 0.43 (0.33, 0.56)
2 26/33 (78.8) 10/17 (58.8) 0.18 (0.08, 0.38)
Age
< 65 years 62/96 (64.6) 15/39 (38.5) 0.42 (0.23, 0.76)
>=65 years 192/289 (66.4) 78/157 (49.7) 0.40 (0.30, 0.53)
Race
White 224/336 (66.7) 80/166 (48.2) 0.38 (0.29, 0.50)
African American or Black 15/29 (51.7) 4/14 (28.6) 0.72 (0.23, 2.20)
Asian 4/6 (66.7) 4/9 (44.4) 1.50 (0.36, 6.19)
All patients 254/385 (66.0) 93/196 (47.4) 0.40 (0.31, 0.52)
0.125 0.25 0.5 1 2 4 8
Subgoup | Lu-PSMA-617 +BSC/BSoC (N=385) n / N (%) | BSC/BSoC only (N=196) n / N (%) | Favors Lu-PSMA-617 | Favors BSC/BSoC | Hazard Ratio Estimate (95% CI)
Region
North America 163/249 (65.5) 60/130 (46.2) 0.39 (0.28, 0.53)
Europe 91/136 (66.9) 33/66 (50.0) 0.43 (0.28, 0.65)
Baseline PSADT
>0 - <=9 months 110/175 (62.9) 40/73 (54.8) 0.37 (0.25, 0.55)
>9 months 3/7 (42.9) 2/9 (22.2) 0.82 (0.11, 6.24)
Baseline PSA
<=76.0 (ng/mL) 108/177 (61.0) 35/91 (38.5) 0.45 (0.30, 0.68)
>76.0 (ng/mL) 146/208 (70.2) 58/105 (55.2) 0.38 (0.27, 0.52)
Num. prior NAADs
1 138/209 (66.0) 42/97 (43.3) 0.51 (0.35, 0.73)
>=2 116/176 (65.9) 51/99 (51.5) 0.32 (0.23, 0.45)
Num. prior immunotherapies
0 199/306 (65.0) 65/146 (44.5) 0.44 (0.33, 0.59)
>=1 55/79 (69.6) 28/50 (56.0) 0.33 (0.20, 0.53)
Num. prior taxanes
1 142/224 (63.4) 49/110 (44.5) 0.39 (0.27, 0.54)
>=2 94/134 (70.1) 40/77 (51.9) 0.44 (0.30, 0.66)
All patients 254/385 (66.0) 93/196 (47.4) 0.40 (0.31, 0.52)
0.05 0.1 0.2 0.4 0.6 1 1.5 2 3 4 5 7
Subgoup | Lu-PSMA-617 +BSC/BSoC (N=385) n / N (%) | BSC/BSoC only (N=196) n / N (%) | Favors Lu-PSMA-617 | Favors BSC/BSoC | Hazard Ratio Estimate (95% CI)
Num. prior non-taxanes
0 230/347 (66.3) 88/183 (48.1) 0.41 (0.32, 0.54)
>=1 24/38 (63.2) 5/13 (38.5) 0.20 (0.07, 0.56)
Prior bone sparing agents
Yes 45/66 (68.2) 21/35 (60.0) 0.35 (0.20, 0.62)
No 209/319 (65.5) 72/161 (44.7) 0.42 (0.31, 0.56)
Prior 223-Radium
Yes 43/63 (68.3) 19/36 (52.8) 0.49 (0.28, 0.87)
No 211/322 (65.5) 74/160 (46.3) 0.38 (0.28, 0.50)
Prior PARP inhibitors
Yes 18/24 (75.0) 5/11 (45.5) 0.31 (0.11, 0.89)
No 236/361 (65.4) 88/185 (47.6) 0.41 (0.31, 0.53)
Concurrent NAADs
Yes 122/193 (63.2) 57/124 (46.0) 0.46 (0.33, 0.65)
No 132/192 (68.8) 36/72 (50.0) 0.25 (0.17, 0.38)
Concurrent radiation therapy
Yes 37/49 (75.5) 16/28 (57.1) 0.51 (0.27, 0.94)
No 217/336 (64.6) 77/168 (45.8) 0.39 (0.29, 0.51)
Concurrent bone sparing agents
Yes 122/175 (69.7) 48/96 (50.0) 0.51 (0.36, 0.72)
No 132/210 (62.9) 45/100 (45.0) 0.29 (0.20, 0.42)
All patients 254/385 (66.0) 93/196 (47.4) 0.40 (0.31, 0.52)
0.05 0.1 0.2 0.4 0.6 1 1.5 2 3 4 5 7

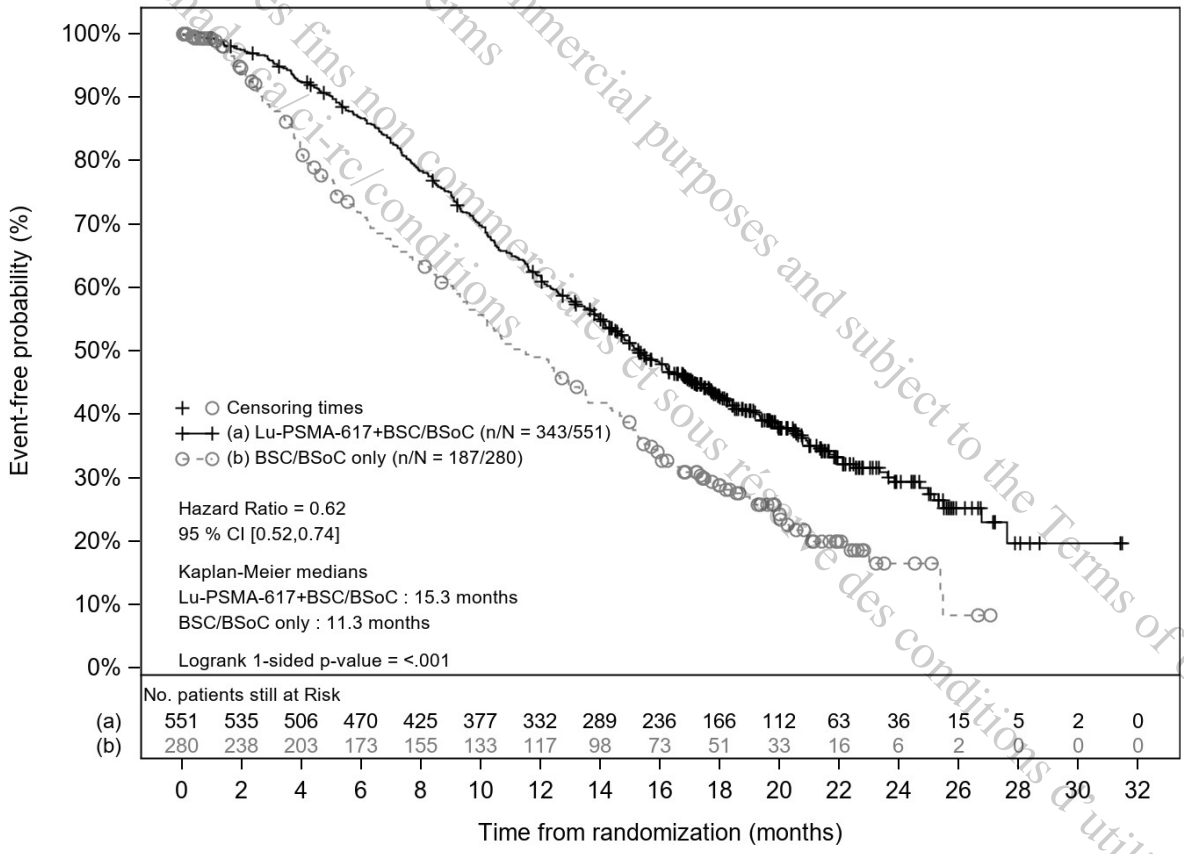
n/N: number of events/number of patients in treatment arm. Vertical line shows no effect point.
Source: [Study PSMA-617-01-Table 14.2.2.2, Table 14.2.2.3, Table 14.2.2.4,Table 14.2.2.5, Table 14.2.2.6, Table 14.2.2.7], [SCE Appendix 1-Figure 2, Table 16, Table 17, Table 18, Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, Table 26, Table 27, Table 28]

The improvement in rPFS observed when adding ^{177}Lu-PSMA-617 to BSC/BSoC to treat these heavily pretreated patients is both statistically significant and clinically compelling in that the benefit is present across all subgroups of enrolled mCRPC patients regardless of age, ECOG status, liver metastases, race and LDH levels, i.e. all factors that are known to complicate patient management. Other treatments (as discussed in Section 6.1.2) have not shown such a delay in disease progression or death in this setting which, as the next section shows, translates into an improvement in OS.

4.3.2.2 Overall survival

For the alternate primary endpoint of OS, an estimated 38% reduction in the risk of death was observed in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (Figure 4-4). This was statistically significant, with a one-sided stratified log-rank test of $p < 0.001$.

Figure 4-4 Study PSMA-617-01: Kaplan-Meier plot of OS (FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score, and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.1.1.1]

The HR was 0.62 (95% CI: 0.52, 0.74) in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only, with a median OS of 15.3 months (95% CI: 14.2, 16.9) and 11.3 months (95% CI: 9.8, 13.5), respectively (Table 4-2). Thus, the median OS was prolonged by 4.0 months.

Table 4-2 Study PSMA-617-01: OS using stratified log-rank test and Cox regression model (FAS)

	^{177}Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280
OS, n (%)		
Deaths	343 (62.3)	187 (66.8)
Censored	208 (37.7)	93 (33.2)
Reasons censored, n (%)		
Alive[1]	189 (34.3)	55 (19.6)
Lost to follow-up[2]	4 (0.7)	5 (1.8)
Withdrew consent[3]	15 (2.7)	33 (11.8)
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	9.0 [7.9, 9.7]	5.1 [4.2, 6.3]
Median OS [95% CI]	15.3 [14.2, 16.9]	11.3 [9.8, 13.5]
75th percentile [95% CI]	26.8 [23.9, NE]	19.8 [17.3, 23.0]
OS rates (%)		
6 months (SE) [95% CI]	86.6 (1.46) [83.5, 89.2]	71.5 (2.86) [65.5, 76.7]
12 months (SE) [95% CI]	61.7 (2.09) [57.5, 65.6]	49.0 (3.21) [42.6, 55.1]
18 months (SE) [95% CI]	43.0 (2.18) [38.7, 47.2]	28.8 (2.98) [23.1, 34.7]
Hazard Ratio (Stratified Cox PH model)[4, 5]	0.62	
95% CI	[0.52, 0.74]	
Stratified Log-rank Test one-sided p-value[5]	<0.001	
Follow-up time (months)[6]		
Median [95% CI]	20.3 [19.8, 21.0]	19.8 [18.3, 20.8]
Minimum-Maximum	0.0 - 31.5	0.0 - 27.1

[1] Patients without event and still on study at data cut-off date.
[2] Patients who discontinued the study for reasons other than withdrew consent.
[3] Patients who withdrew consent from the study.
[4] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[5] Both Cox PH model and Log-rank test are stratified for 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 at time of randomization (yes vs. no). IRT data for stratification are used.
[6] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for deaths.

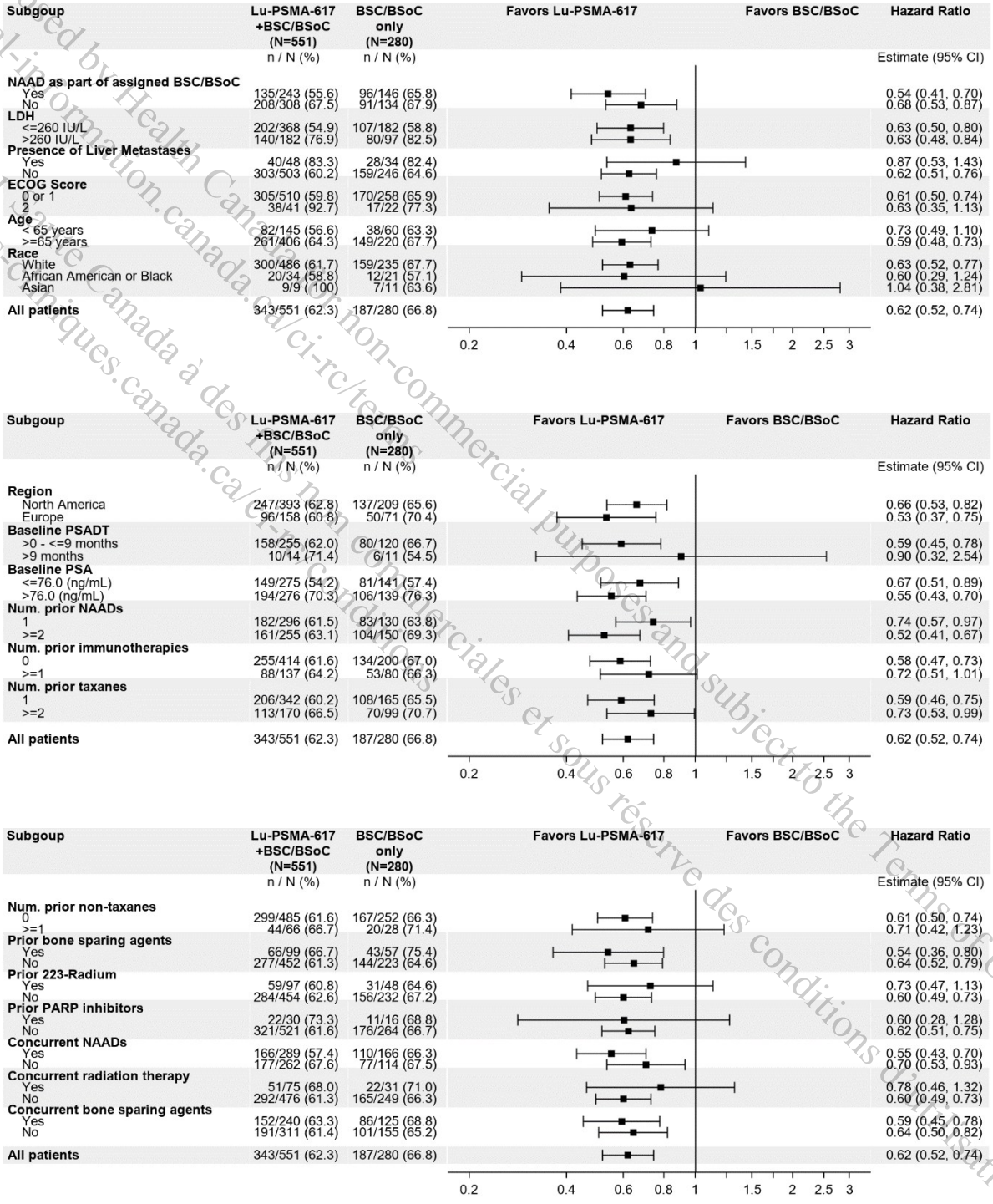
Source: [Study PSMA-617-01-Table 14.2.1.1]

Additional analyses on OS were also performed:

- An OS analysis based on the PFS-FAS population was consistent with the primary analysis [Study PSMA-617-01-Section 11.1.3.2].
- A sensitivity analysis of OS to assess the impact of COVID-19 was also consistent with the primary analysis [Study PSMA-617-01-Table 14.2.1.9].
- An analysis of OS was conducted based on the first 750 patients randomized, and was also consistent with the primary analysis [SCE-Section 3.2.1.2.1].
- A panel of analyses were performed to assess the sensitivity of OS to censoring due to drop-outs. These were also consistent with the primary analysis of OS, and are discussed in Section 4.3.2.3 and presented in detail in [SCE-Table 3-15].

All subgroup analyses of OS were consistent with the primary OS analysis and demonstrate the homogeneity of the treatment effect across these subgroups (Figure 4-5), with the exception of subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and PSADT >9 months subgroups).

Figure 4-5 Study PSMA-617-01: OS treatment effect for patient subgroups - Forest plot of HR with 95% CI (FAS)



Vertical line shows no effect point. n/N: number of events/number of patients in treatment arm. Subgroup classes with at least 10 patients are presented

Source: [Study PSMA-617-01-Table 14.2.1.3, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6, Table 14.2.1.7, Table 14.2.1.8], [SCE Appendix 1-Figure 1, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15]

The improvement in OS observed when adding ^{177}Lu-PSMA-617 to BSC/BSoC to treat these heavily pretreated patients is both statistically significant and clinically compelling, given the limited number of palliative-only management options available to physicians when treating patients with advanced stage mCRPC who have previously received existing medications known to impact survival (e.g., AR pathway inhibitors, taxanes, etc.). Other treatments (as discussed in Section 6.1) have not shown such a survival time in these heavily pretreated patients with progressive PSMA-positive mCRPC. This benefit in survival time, along with the delay in radiographic disease progression or death (Section 4.3.2.1), is also associated with improvements in ORR that were durable, DCR, and time to SSE, as shown in Section 4.3.3.

4.3.2.3 Changes to address the initial high dropout rate

A high dropout rate among patients randomized to BSC/BSoC became evident early in the study. As such, rPFS data could not be collected for these patients, which consequently could result in bias in the analysis of rPFS. Enhanced study site education measures to curtail this phenomenon were implemented and made effective on 05-Mar-2019. In addition, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 05-Mar-2019; therefore, rPFS was to be analyzed in these patients once 364 events had accrued. The OS analyses were performed on all randomized patients. Further details on the operational, statistical, and design-related actions to mitigate the high drop-out rate are discussed in [Study PSMA-617-01-Section-9.2].

In total, 82 patients in the control arm withdrew consent to be treated with BSC/BSoC, and 26 of whom withdrew consent for study participation; 56 patients entered long-term follow up, 48 of whom died and 8 were alive as of the data cut off [SCE Appendix 1-Table 14.2.1.15]. Thirteen patients who withdrew consent to BSC/BSoC treatment received subsequent systemic cancer therapies, which are presented in [SCE Appendix 1-Table 14.3.12.4].

Additional analyses on rPFS and OS were conducted to assess the effect of the changes to the planned analyses. These analyses consist of:

- rPFS based on the FAS [SCE-Section 3.2.1.1.1]
- OS based on the PFS-FAS [SCE-Section 3.2.1.2.2]
- OS based on the first 750 patients randomized [SCE-Section 3.2.1.2.1]

Additionally, a panel of sensitivity analyses to assess the sensitivity of rPFS and OS to censoring due to drop-outs are described in detail in [SCE-Table 3-15].

All these analyses were consistent with the primary analyses of rPFS and OS, and demonstrated that neither the initial high drop-out rate, nor the implemented changes to mitigate it, had an effect on the interpretation or robustness of the study results.

4.3.3 Key secondary efficacy results from Study PSMA-617-01

ORR, DCR, and time to SSE were pre-specified as key secondary endpoints, with multiplicity controlled by a Hochberg closed-test procedure using the α level from a successful OS result.

All key secondary endpoints showed a statistically significant benefit: ORR (29.8% with a durable response, median DoR of 9.8 months), DCR (89.0%), and time to SSE (an estimated 50% reduction in the risk of a SSE or death when compared with BSC/BSoC only) (Table 4-3, Figure 4-6).

Table 4-3 Study PSMA-617-01: key secondary efficacy results

	^{177}Lu-PSMA-617+ BSC/BSoC	BSC/BSoC only
Response evaluable analysis set	**N=319**	**N=120**
Overall Response Rate (ORR: CR+PR), n (%)	95 (29.8)	2 (1.7)
Odds Ratio [95% CI][1]	24.99 [6.05, 103.24]	
Two-sided p-value[1]	< 0.001	
Disease Control Rate (DCR CR+PR+SD+Non-CR/ Non-PD > 6 weeks), n (%)	284 (89.0)	80 (66.7)
Odds Ratio [95% CI][1]	5.79 [3.18, 10.55]	
Two-sided p-value[1]	< 0.001	
Duration of Response (DoR) (months), n (%)[2]		
KM Median DoR [95% CI]	9.8 [9.1, 11.7]	10.6 [NE, NE]
PFS-FAS set	**N=385**	**N=196**
Time to symptomatic skeletal event (SSE), n (%)		
KM Median time to SSE [95% CI]	11.5 [10.3, 13.2]	6.8 [5.2, 8.5]
Hazard Ratio (Stratified Cox PH model)[3, 4]	0.50	
95% CI	[0.40, 0.62]	

[1] Odds Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only based on logistic regression model stratifying for the randomization stratification factors, 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 at time of randomization (yes vs. no). IRT data for stratification are used. P-value based on Wald's Chi-Square test.

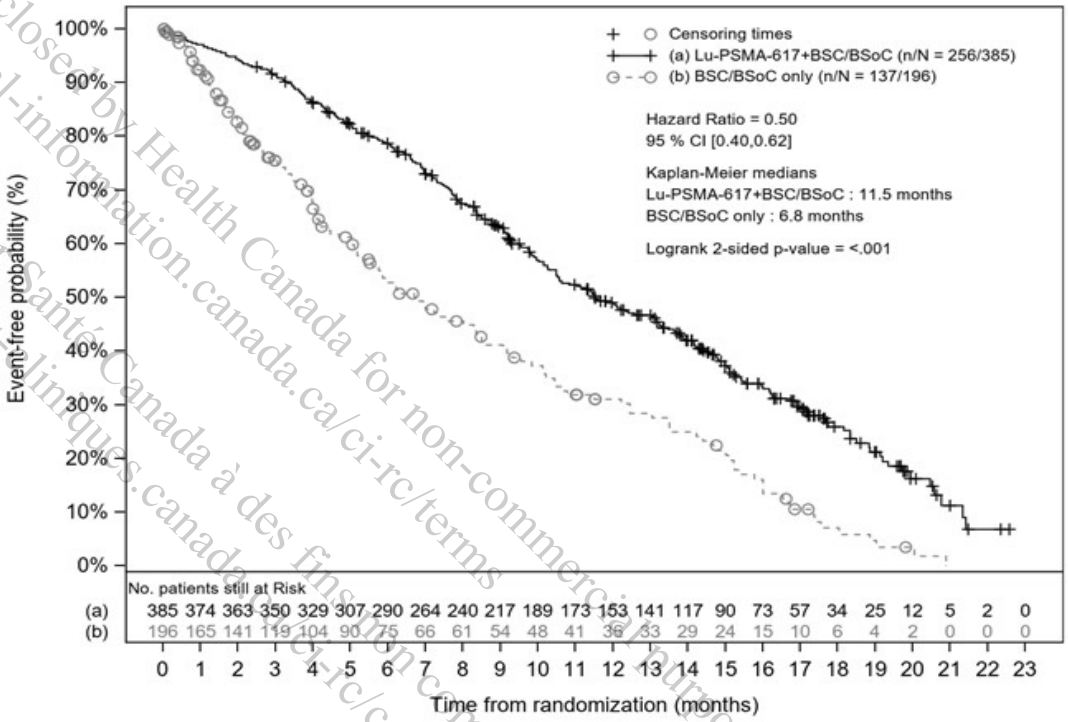
[2] DoR is not a key secondary endpoint

[3] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.

[4] Cox PH model is stratified for 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 at time of randomization (yes vs. no). IRT data for stratification are used patients (months); SE: standard error; EDoR: expected duration of response (months) equals Mean DoR X Overall Response Rate.

Source: [Study PSMA-617-01-Table 14.2.3.1], [Study PSMA-617-01-Table 14.2.4.1]

Figure 4-6 Kaplan-Meier plot of time to SSE (PFS-FAS)



Stratified log-rank test and stratified Cox model using strata per IRT defined by LDH level, presence of liver metastases, ECOG score and inclusion of NAAD in BSC/BSoC at time of randomization.
n/N: number of events/number of patients in treatment arm.
Source: [Study PSMA-617-01-Figure 14.2.3.2]

A delay of disease progression is seen by patients as a surrogate for longevity, and a delay in disease progression provides many patients with an enhanced sense of well-being despite having an incurable disease. Since many other therapies have failed by this stage of disease management (discussed in Section 6.1.2), the ability to control disease progression in this heavily pretreated population is of clinical importance. The longer time to occurrence of a SSE is also beneficial, since it enables continued ambulation and freedom of movement in these patients. These improvements are accompanied by improvements in PFS, biochemical response, and PROs, as discussed in the next section.

4.3.4 Additional secondary efficacy results from Study PSMA-617-01

The additional secondary efficacy endpoints of PFS, biochemical response assessments, and PROs further show the utility of treatment with ^{177}Lu-PSMA-617+BSC/BSoC.

PFS analyses showed an estimated 70% risk reduction of radiographic disease progression, clinical progression, PSA progression, or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR = 0.30; 95% CI: 0.24, 0.38). The median PFS was 5.9 months (95% CI: 5.2, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.4 months (95% CI: 2.2, 3.0) in the BSC/BSoC only arm [Study PSMA-617-01-Section 11.2.2.1].

Biochemical response was assessed by evaluating changes in PSA, ALP and LDH levels [Study PSMA-617-01-Section 11.2.2.2]:

- The mean PSA doubling time in patients with a PSA increase was in favor of the ^{177}Lu-PSMA-617+ BSC/BSoC arm: 20.1 months (95% CI: 11.5, 28.6) vs. 12.4 months (95% CI: 7.9, 16.9) in the BSC/BSoC only arm. However, it should be noted that there was an imbalance between the two treatment arms in the numbers of evaluable patients (73.8% vs. 37.8%, respectively).
- PSA response, defined as a ≥ 50% decrease from baseline, occurred in more patients (46.0%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (7.1%).
- Mean and median baseline PSA levels were similar in both arms, while the best percentage change from baseline was larger in the ^{177}Lu-PSMA-617+ BSC/BSoC arm (mean and median decreases of -20.9% and -68.6%) than in the BSC/BSoC only arm (50.4% and 24.3%).
- Mean and median baseline ALP levels were similar in both arms, while the best percentage change from baseline was larger in the ^{177}Lu-PSMA-617+ BSC/BSoC arm (mean and median decreases of -14.4% and -17.0%) than in the BSC/BSoC only arm (mean increase of 0.6% and median decrease of -5.0%).
- Mean and median baseline LDH levels were similar in both arms, while the best percentage change from baseline was larger in the ^{177}Lu-PSMA-617+ BSC/BSoC arm (mean and median decreases of -23.1% and -23.3%) than in the BSC/BSoC only arm (-9.2% and -12.6%).

PRO results suggest that the patients' quality of life was more stable from cycle to cycle in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm. While both treatment arms trended flat, there was more variability observed in the BSC/BSoC only arm [Study PSMA-617-01-Section 11.2.2.3]:

- FACT-P total score showed an estimated 46% risk reduction in worsening from baseline, clinical progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm across its many subscales and components.
- There was a delayed time to worsening of the FACT-P total score with a median time of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm.
- BPI-SF showed that patients were more stable with less pain and lower interference with daily activities in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with the BSC/BSoC only arm experiencing a greater degree of variation.
    - For the BPI-SF pain intensity scale: there was an estimated 48% reduction in risk of worsening, clinical progression or death (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm
    - For the BPI-SF pain interference scale: there was an estimated 43% reduction in risk of worsening, clinical progression or death (HR = 0.57; 95% CI: 0.47, 0.69; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm

The improvement in PFS, along with biochemical responses and PRO results adds to the overall benefit of a lower risk of both disease progression or death, as previously discussed.

4.4 Long-term data, development of tolerance, or withdrawal effects

^{177}Lu-PSMA-617 is not intended for long-term use. As such, no data on long-term use, the development of tolerance, or withdrawal effects are available.

4.5 Efficacy conclusions

Substantial evidence of the efficacy of ^{177}Lu-PSMA-617+BSC/BSoC in mCRPC is provided from the Phase III Study PSMA-617-01. This study shows that adding ^{177}Lu-PSMA-617 every 6 weeks (± 1 week) to BSC/BSoC for 6 cycles (described in Section 4.1) in the clinical management of heavily pretreated patients with progressive PSMA-positive mCRPC (described in Section 4.3.1) has led to:

- An estimated 60% reduction in the risk of radiographic disease progression or death when compared with BSC/BSoC only (described in Section 4.3.2.1)
  - A median rPFS prolongation of 5.3 months was observed: from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
- An estimated 38% reduction in the risk of death when compared with BSC/BSoC only (described in Section 4.3.2.2)
  - A median OS prolongation of 4.0 months was observed: from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
- A statistically significant benefit in all key secondary endpoints: ORR (29.8% with a durable response, median DoR of 9.8 months), DCR (89.0%), and time to SSE (an estimated 50% reduction in the risk of a SSE or death when compared with BSC/BSoC only) (described in Section 4.3.3)
- An improvement in PFS, biochemical responses, and PRO results (described in Section 4.3.4)

When taken as a whole, these statistically significant results demonstrate a clinically meaningful improvement for men with advanced stage mCRPC over current therapeutic options, where "clinically meaningful" is defined as:

- An HR ≤ 0.8 corresponding to an improvement in median OS within the range of 2.5 to 6 months
- Incremental gains in other efficacy and key secondary endpoints
- Minimal increase in toxicity compared to prevailing therapies (i.e. taxane- or platinum-based regimens) (as discussed in Section 5).

These are further discussed in the context of the overall benefit-risk profile for ^{177}Lu-PSMA-617 in Section 6.

5 Overview of safety

This section provides an overview of the two prospective clinical studies supporting the safety evaluation of ^{177}Lu-PSMA-617 (studies PSMA-617-01 and PSMA-617-02). Their study designs are summarized in Table 1-1 and are described further in the individual CSRs. A full systematic review of the safety results of these two studies is provided in the [SCS].

Safety data derived from these two studies show an well-tolerated and manageable safety profile for ^{177}Lu-PSMA-617.

5.1 Safety population, evaluations, and patient exposure

5.1.1 Safety population

The main safety evaluation was based on data from the pivotal registration study, PSMA-617-01, and a supportive study, PSMA-617-02, which were both performed in the target indication of PSMA-positive mCRPC.

No pooling of safety data across these studies was performed due to differences between the two studies (such as study design, treatment regimen, safety data collection processes).

In Study PSMA-617-01, the FAS-Safety analysis set comprised 529 patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm (who were treated with at least one non-zero dose of ^{177}Lu-PSMA-617), and 205 patients in the BSC/BSoC only arm.

In Study PSMA-617-02, the Safety Population comprised 23 patients in the 6.0 GBq ^{177}Lu-PSMA-617 group, and 41 patients in the 7.4 GBq ^{177}Lu-PSMA-617 group. Since patients in this study did not consistently receive BSoC along with ^{177}Lu-PSMA-617, data from these patients are presented separately as supportive safety evidence.

5.1.2 Evaluations

In Study PSMA-617-01, ^{177}Lu-PSMA-617 was evaluated for the following:

- Frequency, type (by SOC and PT), severity, and causal relationship of AEs to study drug
- Deaths, frequency of SAEs, AESIs, AEs leading to discontinuation, and AEs requiring dose reduction and/or interruption
- Changes in clinical laboratory values observed after regular monitoring of hematology and clinical chemistry
- Regular assessments of vital signs.

Further details can be found in [Study PSMA-617-01-Section 9.5.4].

In Study PSMA-617-02, similar safety evaluations were also performed. However, key differences were that AESI categories had not been defined while these data were analyzed, and only SAEs were graded using CTCAE.

In both studies, AEs were coded using MedDRA. As these studies were conducted at different time points across an extended period, different versions of MedDRA and CTCAE were used for the safety evaluations [SCS-Section 2.1].

The nature and timing of the clinical monitoring for AEs was considered to be adequate for the expected toxicities associated with ^{177}Lu-PSMA-617 therapy. Patients were indirectly questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by patients during or between clinic visits or through physical examination, laboratory test results, or other assessments.

In addition to the standard safety evaluations outlined above, several AE categories warranting closer scrutiny were pre-identified during the development program. These AESIs were selected based on the mechanism of action of ^{177}Lu-PSMA-617 and biological plausibility, as well as nonclinical observations.

5.1.3 Patient exposure

In Study PSMA-617-01, the exposure to ^{177}Lu-PSMA-617 was considered appropriate to allow for an adequate assessment of safety in patients who were representative of the intended target population. In the ^{177}Lu-PSMA-617+BSC/BSoC arm, 46.5% of the patients received 6 cycles of ^{177}Lu-PSMA-617, the maximum number of cycles planned per protocol, and 67.7% received at least 4 cycles, the minimum recommended per protocol. The mean dose intensity was 5.5 (SD ±1.2) GBq/month, and the mean cumulative dose was 33.4 GBq (SD ±12.8) [Study PSMA-617-01-Section 10.5.1.2.2].

In Study PSMA-617-02, patients received their intended dose for each cycle as per the protocol. Almost half of the patients in each treatment group received 4 cycles (43.5% in the 6.0 GBq group, and 46.3% in the 7.4 GBq group). The mean cumulative dose for the 6.0 GBq group was 16.9 GBq (SD ±7.6), and 21.4 GBq (SD ±8.03) for the 7.4 GBq group [Study PSMA-617-02-Section 12.1.1].

5.2 Adverse events

5.2.1 Most frequently occurring AEs

The most frequently reported AEs were consistent with those previously reported, and were considered tolerable and manageable with standard clinical interventions.

In Study PSMA-617-01, differences between the two treatment arms with an incidence of ≥ 10% were observed for fatigue, dry mouth, nausea, anemia, diarrhea, vomiting, thrombocytopenia, lymphopenia, leukopenia, and urinary tract infection (Table 5-1). In both arms, individual AE PTs ≥ grade 3 were infrequently reported, except for anemia, thrombocytopenia, lymphopenia, and fatigue, which are expected for ^{177}Lu-PSMA-617 [Study PSMA-617-01-Section 12.1.2.2.2].

Table 5-1 Study PSMA-617-01: AEs occurring in at least 5.0% of patients in either arm during randomized treatment by preferred term and maximum grade (FAS-Safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Patients with at least one event	**519 (98.1)**	**279 (52.7)**	**170 (82.9)**	**78 (38.0)**
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anaemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhoea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Bone pain	59 (11.2)	13 (2.5)	17 (8.3)	5 (2.4)
Urinary tract infection	58 (11.0)	20 (3.8)	2 (1.0)	1 (0.5)
Weight decreased	57 (10.8)	2 (0.4)	18 (8.8)	0
Dyspnoea	53 (10.0)	7 (1.3)	20 (9.8)	3 (1.5)
Oedema peripheral	51 (9.6)	2 (0.4)	13 (6.3)	0
Haematuria	45 (8.5)	13 (2.5)	9 (4.4)	1 (0.5)
Neutropenia	45 (8.5)	18 (3.4)	3 (1.5)	1 (0.5)
Pain in extremity	45 (8.5)	3 (0.6)	12 (5.9)	0
Dizziness	44 (8.3)	5 (0.9)	9 (4.4)	0
Cough	42 (7.9)	0	13 (6.3)	0
Hypokalaemia	40 (7.6)	5 (0.9)	8 (3.9)	0
Fall	38 (7.2)	1 (0.2)	12 (5.9)	2 (1.0)
Headache	37 (7.0)	4 (0.8)	4 (2.0)	0
Hypocalcaemia	36 (6.8)	4 (0.8)	7 (3.4)	1 (0.5)
Pyrexia	36 (6.8)	2 (0.4)	7 (3.4)	0
Asthenia	34 (6.4)	6 (1.1)	16 (7.8)	2 (1.0)
Pain	33 (6.2)	7 (1.3)	9 (4.4)	1 (0.5)
Abdominal pain	32 (6.0)	5 (0.9)	7 (3.4)	1 (0.5)
Hypertension	30 (5.7)	17 (3.2)	12 (5.9)	3 (1.5)
Blood creatinine increased	28 (5.3)	1 (0.2)	5 (2.4)	1 (0.5)
Hypophosphataemia	28 (5.3)	5 (0.9)	7 (3.4)	1 (0.5)
Insomnia	28 (5.3)	0	9 (4.4)	0
Spinal cord compression	7 (1.3)	7 (1.3)	11 (5.4)	11 (5.4)

Source: [Study PSMA-617-01-Table 14.3.2.13.2]

In Study PSMA-617-02, the frequently reported TEAEs were similar as in Study PSMA-617-01: dry mouth (47.8% of patients in the 6.0 GBq group vs. 63.4% of patients in the 7.4 GBq group); fatigue (56.5% in the 6.0 GBq group vs. 51.2% in the 7.4 GBq group); and nausea (52.2% in the 6.0 GBq group vs. 43.9% in the 7.4 GBq group). Notably, none of these events were severe, except for 1 event of nausea in the 7.4 GBq treatment group [Study PSMA-617-02-Section 12.2.2.2].

5.2.2 Deaths and other serious or clinically relevant adverse events

5.2.2.1 Deaths

Overall, few deaths were reported to be related to treatment with ^{177}Lu-PSMA-617. Deaths were typically attributed to either disease progression, or to conditions commonly seen in this patient population.

In Study PSMA-617-01, the most frequent primary cause for death was disease progression (8.3% in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 6.8% in the BSC/BSoC only arm). SAEs with fatal outcome were reported in 19 patients (3.6%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (including 1 disease progression and 1 death due to COVID-19) and in 6 patients (2.9%) in the BSC/BSoC arm (including 1 disease progression). The only PTs that were reported more than once in either arm were sepsis (4 patients, 0.8%) and pancytopenia (2 patients, 0.4%), all reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Three deaths were reported to be related to study treatment: 2 events of pancytopenia and one event of bone marrow failure, all reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Upon medical review, the one death due to bone marrow failure reported by the investigator as related to study treatment was not considered related to ^{177}Lu-PSMA-617 treatment. Overall, no apparent patterns in the nature of these fatal events was observed [Study PSMA-617-01-Section 12.2.1].

In Study PSMA-617-02, 3 patients (4.7%) died due to fatal TEAEs, of which 2 deaths were considered possibly related to the study treatment. Two (8.7%) of these patients were in the 6.0 GBq group: one died due to a subdural hematoma 94 days after the last dose, which was determined to be possibly related; and one died due to metastases to the CNS 68 days after the last dose, which was determined to be unrelated. One patient (2.4%) in the 7.4 GBq group died due to gastrointestinal hemorrhage and unknown causes 72 days after the last dose, which was determined to be possibly related [Study PSMA-617-02-Section 12.3.1].

5.2.2.2 Serious adverse events

Individual SAEs were infrequently reported in both studies.

In Study PSMA-617-01, SAEs occurring in at least 3 patients in either arm during randomized treatment are presented in Table 5-2. In either arm, each SAE was reported with a frequency < 3.0% except for spinal cord compression which was reported in 4.9% of patients in the BSC/BSoC only arm (vs. 1.1% in the ^{177}Lu-PSMA-617+BSC/BSoC arm).

Table 5-2 Study PSMA-617-01: SAEs occurring in at least 3 patients in either arm during randomized treatment (FAS-Safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	**192 (36.3)**	**169 (31.9)**	**57 (27.8)**	**52 (25.4)**
Anaemia	15 (2.8)	14 (2.6)	1 (0.5)	0
Urinary tract infection	13 (2.5)	13 (2.5)	1 (0.5)	1 (0.5)
Haematuria	11 (2.1)	10 (1.9)	1 (0.5)	1 (0.5)
Sepsis	10 (1.9)	9 (1.7)	2 (1.0)	2 (1.0)
Acute kidney injury	9 (1.7)	8 (1.5)	6 (2.9)	5 (2.4)
Back pain	9 (1.7)	7 (1.3)	3 (1.5)	3 (1.5)
Pneumonia	7 (1.3)	7 (1.3)	3 (1.5)	2 (1.0)
Pyrexia	7 (1.3)	1 (0.2)	0	0
Bone pain	6 (1.1)	5 (0.9)	2 (1.0)	2 (1.0)
Pancytopenia	6 (1.1)	6 (1.1)	0	0
Pulmonary embolism	6 (1.1)	6 (1.1)	2 (1.0)	2 (1.0)
Spinal cord compression	6 (1.1)	6 (1.1)	10 (4.9)	10 (4.9)
Constipation	5 (0.9)	4 (0.8)	1 (0.5)	1 (0.5)
Dehydration	5 (0.9)	5 (0.9)	1 (0.5)	1 (0.5)
Dyspnoea	5 (0.9)	2 (0.4)	1 (0.5)	1 (0.5)
Pain	5 (0.9)	5 (0.9)	1 (0.5)	1 (0.5)
Urinary retention	5 (0.9)	4 (0.8)	2 (1.0)	1 (0.5)
Vomiting	5 (0.9)	3 (0.6)	1 (0.5)	1 (0.5)
Abdominal pain	4 (0.8)	3 (0.6)	1 (0.5)	1 (0.5)
Hypotension	4 (0.8)	3 (0.6)	0	0
Subdural haematoma	4 (0.8)	4 (0.8)	2 (1.0)	2 (1.0)
Syncope	4 (0.8)	4 (0.8)	0	0
Urinary tract obstruction	4 (0.8)	4 (0.8)	0	0
Deep vein thrombosis	3 (0.6)	2 (0.4)	0	0
Infection	3 (0.6)	3 (0.6)	2 (1.0)	2 (1.0)
Ischaemic stroke	3 (0.6)	2 (0.4)	0	0
Mental status changes	3 (0.6)	2 (0.4)	0	0
Nausea	3 (0.6)	2 (0.4)	1 (0.5)	1 (0.5)
Thrombocytopenia	3 (0.6)	3 (0.6)	0	0
Urosepsis	3 (0.6)	3 (0.6)	0	0

Source: [Study PSMA-617-01-Table 14.3.2.13.3]

In Study PSMA-617-02, SAEs were reported for 4 patients (17.4%) in the 6.0 GBq group and for 8 patients (19.5%) in the 7.4 GBq group. Overall, the single most frequently reported SAE was metastases to the CNS, occurring in 2 patients (3.1%), both in the 6.0 GBq group. All other SAE PTs occurred in only one patient each [Study PSMA-617-02-Section 12.3.2].

5.2.2.3 Adverse events leading to permanent discontinuation, dose interruption, or reduction of ^{177}Lu-PSMA-617

Treatment with ^{177}Lu-PSMA-617+BSC/BSoC was manageable and well-tolerated, with few AEs leading to permanent discontinuation, dose interruption, or reduction of ^{177}Lu-PSMA-617.

In Study PSMA-617-01, AEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 were infrequent, with 63 patients (11.9%) discontinuing ^{177}Lu-PSMA-617+BSC/BSoC due to AEs. The most frequent events were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (1.3%). All other events were reported in less than 1% of patients [Study PSMA-617-01-Section 12.2.3]. The most frequent events that led to dose interruption or reduction of ^{177}Lu-PSMA-617 were anemia (5.1%, 1.3%) and thrombocytopenia (3.6%, 1.9%). All other events were reported for less than 2.0% of patients [Study PSMA-617-01-Section 12.2.4].

In Study PSMA-617-02, only one TEAE led to the discontinuation of ^{177}Lu-PSMA-617. Abdominal pain was reported in 1 patient (2.4%) in the 7.4 GBq group [Study PSMA-617-02-Section 12.3.4]. TEAEs leading to dose reduction of ^{177}Lu-PSMA-617 were reported for 2 patients (4.9%), these 2 events of anemia occurred in the 7.4 GBq group [Study PSMA-617-02-Section 12.3.5].

5.2.2.4 Clinical hematology

In Study PSMA-617-01, hematology abnormalities were more frequent and usually of higher grade in the ^{177}Lu-PSMA-617+BSC/BSoC arm, as reflected in the incidences of TEAEs related to myelosuppression. Of note, during long-term follow-up, these hematology abnormalities in the ^{177}Lu-PSMA-617+BSC/BSoC arm returned to similar incidences and severity to what was seen in the BSC/BSoC only arm. Generally, the shifts from baseline values to higher grades for hematology abnormalities were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm, as compared to the BSC/BSoC only arm (shifts were lower and with relatively fewer or no shifts to grade 3 or 4) [SCS-Section-3.2.1].

In Study PSMA-617-02, the clinical hematology results were comparable with the PSMA-617-01 study results [SCS-Section-3.2.1.2].

5.2.2.5 Clinical chemistry

In Study PSMA-617-01, biochemistry values and categorical analysis of hepatic laboratory values were similar in both treatment arms. For both treatment arms and all parameters analyzed for subgroups, almost all patients had normal or low grade clinical chemistry laboratory abnormalities (grade 1 or 2) at baseline. During treatment, only few shifts to higher grades were observed; however, there was no clear trend; and none of these shifts raised any specific safety concerns [SCS-Section-3.2.2].

In Study PSMA-617-02, the clinical chemistry results were comparable with the PSMA-617-01 study results [SCS-Section-3.2.2].

5.2.2.6 Vital signs

In Study PSMA-617-01, notable vital signs for blood pressure, pulse rate and weight during randomized treatment were observed in <10% patients, except for a weight decrease by >10%

from baseline observed in 12.9% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm as compared with 5.9% patients in the BSC/BSoC only arm [SCS-Section-4.1.1].

In Study PSMA-617-02, no clinically relevant changes in vital signs were observed in the mean values during the study when comparing post-baseline values with baseline values; and during the cycles when comparing post-treatment values with pre-treatment values [SCS-Section-4.1.2].

5.2.2.7 Electrocardiograms

In Study PSMA-617-01, ECGs were performed at screening only. However, as a response to HA advice to consider the collection of ECG data at baseline and after treatment with ^{177}Lu-PSMA-617, a sub-study was performed in a non-randomized single-arm cohort (^{177}Lu-PSMA-617+BSC/BSoC) of 30 patients at sites in Germany.

^{177}Lu-PSMA-617 had no effects on heart rate, PR interval, or QRS duration; however, 1 patient developed a new anterior T wave inversion of unclear clinical significance. These analyses demonstrated no effects of ^{177}Lu-PSMA-617 on QTcF [SCS-Section-4.2.1].

In Study PSMA-617-02, no clinically significant abnormalities in ECG results were observed [SCS-Section-4.2.2].

5.3 Safety topics of interest

Overall, no new or unexpected safety concerns were observed for the safety topics of interest (defined in [SCS-Section-2.1.5.1.1]). This section focuses on two safety topics of interest requested during Health Authority guidance, plus AESIs. All other safety topics of interest are summarized in Table 5-3, and are discussed in detail in [SCS-Section-2.1.5.1].

Table 5-3 Study PSMA-617-01: overview of safety topics of interest by category and maximum grade (FAS-Safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Safety topic	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Fatigue	260 (49.1)	37 (7.0)	60 (29.3)	5 (2.4)
Myelosuppression	251 (47.4)	124 (23.4)	36 (17.6)	14 (6.8)
Dry mouth	208 (39.3)	0	2 (1.0)	0
Nausea and Vomiting	208 (39.3)	8 (1.5)	35 (17.1)	1 (0.5)
Hepatotoxicity	54 (10.2)	15 (2.8)	16 (7.8)	5 (2.4)
Renal effects	46 (8.7)	18 (3.4)	12 (5.9)	6 (2.9)
Second primary malignancies	11 (2.1)	4 (0.8)	2 (1.0)	1 (0.5)
QT prolongation	9 (1.7)	7 (1.3)	1 (0.5)	1 (0.5)
Intracranial haemorrhage	7 (1.3)	5 (0.9)	3 (1.5)	2 (1.0)
Reproductive toxicity	1 (0.2)	1 (0.2)	0	0

Source: [Study PSMA-617-01-Table 14.3.3.4.1]

Dry Eye: was reported by 16 patients (3.0%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 2 patients (1.0%) in the BSC/BSoC only arm. These were all grade 1 events, except for 1 grade 2 event in 1 patient in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Grade 1 events were defined as asymptomatic where lubricants were sufficient (as per CTCAE v5.0). Three patients (0.6%) received artificial tears as concomitant medication. Grade 2 events were defined as symptomatic with moderate decrease in visual acuity (as per CTCAE v5.0). The single grade 2 event occurred in an [40-94]-year-old patient on study day 158, and was still ongoing at the latest observation. The patient had no other eye- or vision-related AEs [SCS-Section 2.1.5.1.2]. Overall, the analysis shows that dry eye is an infrequent event for patients on ^{177}Lu-PSMA-617 treatment, nearly always asymptomatic and manageable with little impact on quality of life.

Dry Mouth: was reported by 208 patients (39.3%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 2 patients (1.0%) in the BSC/BSoC only arm. The majority of events (33.3%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm were grade 1, defined as symptomatic (e.g, dry or thick saliva) but without significant alteration of diet (as per CTCAE v5.0). Thirty patients (5.7%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm had grade 2 events, defined as moderate symptoms implying some alterations of oral intake such as copious water, other lubricants, soft or pureed foods (as per CTCAE v5.0). There were no records of artificial saliva products being administered as concomitant medication in the study, suggesting uncomplicated symptom management in these cases. The generally good tolerability of this safety topic is attested by the infrequent treatment discontinuation: the ^{177}Lu-PSMA-617 dose was reduced in 3 patients (0.6%), and was discontinued in 1 patient (0.2%) [SCS-Section 2.1.5.1.2].

An analysis of other AEs that may suggest complications of dry mouth that could impact morbidity and quality of life was performed. Dental caries AEs were experienced by 4 patients (0.8%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and in no patients in the BSC/BSoC only arm. All four of these patients had also reported an AE of dry mouth. The dental caries were resolved in 3 cases of grade 1 dry mouth, and was still ongoing at the last observation in 1 patient with grade 2 dry mouth. Stomatitis was reported as an AE in 9 patients (1.7%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and in no patients in the BSC/BSoC only arm. Six of these 9 patients reported dry mouth during the study (three grade 2 and three grade 1 AEs). There was 1 SAE of grade 3 stomatitis (and was still ongoing at the last observation); however, this occurred in a patient who did not have dry mouth. The other events were grades 1-2; 4 resolved and 4 were ongoing [SCS-Section 2.1.5.1.2].

Overall, the analysis suggests that dry mouth, although a frequent event for patients on ^{177}Lu-PSMA-617 treatment, is a readily manageable event with little impact on morbidity and quality of life and infrequently results in discontinuation of treatment.

5.3.1 Adverse events of special interest

As treatment with ^{177}Lu-PSMA-617 is already known to increase risk of dry mouth (discussed above), fatigue, myelosuppression (including anemia, thrombocytopenia, lymphopenia, and leukopenia), renal effects, and nausea and vomiting, these adverse events of special interest are discussed further.

In Study PSMA-617-01, imbalances between the two treatment arms were observed in the incidence of the following AESIs (Table 5-3):

- Fatigue (49.1% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 29.3% of patients in the BSC/BSoC only arm), myelosuppression (47.4% vs. 17.6%), dry mouth (39.3% vs. 1.0%, discussed above), and nausea and vomiting (39.3% vs. 17.1%). Of note, some of these adverse events were high grade in severity, but generally few (< 0.5%) led to discontinuation of ^{177}Lu-PSMA-617, except for myelosuppression (in 7.0% of patients).

Other AESIs showed smaller differences between the treatment arms:

- Renal effects (8.7% of patients vs. 5.9% of patients) was reported with a comparable incidence in both treatment arms.

Overall, the data show that these events were manageable, often transient allowing continuation of treatment with supportive care, and only caused a few delays in treatment cycles. AESIs in Study PSMA-617-01 are further discussed in [SCS-Section 2.1.5.1].

In Study PSMA-617-02, despite earlier results of the study not presenting safety with the AESI groupings defined for Study PSMA-617-01, corresponding safety results appear broadly comparable [SCS-Section 2.1.5.2]. In the 28 patients in the 6.0 GBq group, and in the 43 patients in the 7.4 GBq group:

- The events of dry mouth (57.8%), fatigue (53.1%), and nausea (46.9%) were the most frequently reported TEAEs overall, with no differences observed between the 2 treatment arms with the exception of dry mouth (47.8% in the 6.0 GBq group vs. 63.4% in the 7.4 GBq group). Notably, none of these events were severe, except for 1 event of nausea in the 7.4 GBq group:
- General incidence of myelosuppression (anemia, thrombocytopenia, lymphopenia, and leukopenia) was low:
  - Anemia was reported in 17.4% of patients in the 6.0 GBq group vs. 9.4% of patients in the 7.4 GBq group. None of these events were severe.
  - One patient (1.6%) had a grade 3 hematologic toxicity (7.4 GBq group).
  - One patient (1.6%) had a drug-related SAE of thrombocytopenia (7.4 GBq group).
  - No lymphopenia or leukopenia events were observed.
- No safety concerns regarding renal toxicity were observed.

5.3.2 Pregnancy

The safety and efficacy of ^{177}Lu-PSMA-617 have not been established in females as ^{177}Lu-PSMA-617 is not indicated for use in females. Therefore, there are no available data on the use of ^{177}Lu-PSMA-617 in pregnant or lactating women. However, based on its mechanism of action, all radiopharmaceuticals, including ^{177}Lu-PSMA-617, can cause fetal harm. It is noted that Study PSMA-617-01 had no reports of partner pregnancies during the randomized treatment period or the long-term follow-up period.

There are no human or animal studies conducted to determine the effects of ^{177}Lu-PSMA-617 on fertility. However, dosimetry data from the PSMA-617-01 sub-study could be utilized to estimate potential effects on male fertility with ^{177}Lu-PSMA-617 treatment. The mean radiation absorbed dose to the testes was 0.023 Gy/GBq, which could result in an estimated mean radiation exposure of 0.17 Gy from a single 7.4 GBq dose and an estimated cumulative mean radiation exposure of 1.02 Gy from six total 7.4 GBq doses. Therefore, for the range of 1

to 6 doses of exposure to ^{177}Lu-PSMA-617 treatment, the threshold for temporary male sterility (0.15 Gy) could may be exceeded (International Commission on Radiological Protection 2007) and ^{177}Lu-PSMA-617 may cause temporary infertility. If the maximum radiation absorbed dose to the testes (0.14 Gy/GBq) is considered, this could result in an estimated radiation exposure of 1.04 Gy from a single 7.4 GBq dose and an estimated cumulative radiation exposure of 6.22 Gy from six total 7.4 GBq doses. Therefore, for the range of 1 to 6 doses of exposure to ^{177}Lu-PSMA-617 treatment, the threshold for permanent male sterility (3.5-6.0 Gy) may possibly be exceeded (International Commission on Radiological Protection 2007), and the possibility that treatment with ^{177}Lu-PSMA-617 may cause permanent infertility cannot be ruled out. Thus, it can be concluded that the recommended cumulative dose of 44.4 GBq of ^{177}Lu-PSMA-617 results in a radiation absorbed dose to the testes within the range where ^{177}Lu-PSMA-617 may cause infertility [SCP-Section 3.1].

Because of its mechanism of action, male patients should use condoms for intercourse during treatment with ^{177}Lu-PSMA-617 and for 14 weeks after the last dose. The proposed contraception timeframe after stopping treatment is based on 5 times the effective half-life of ^{177}Lu-PSMA-617, plus an additional 3 months (90 days) to take into account the duration of the full spermatogenesis cycle. The effective half-life (Te) is calculated using both the physical half-life (Tp) of the lutetium radionuclide (6.647 days) and the biological half-life (Tb) of ^{177}Lu-PSMA-617 (geometric mean terminal elimination half-life of 41.6 h). The effective half-life (Te) is calculated to be 33 hours or ~1.4 days, using the equation 1/Te = (1/Tp) + (1/Tb). Therefore, the proposed post-dose timeframe for male contraception is 90 days plus 7 days (5 effective half lives = 5*1.4 days = 7 days), which totals 97 days or rounded up to ~14 weeks [SCP-Section 3.1].

5.3.3 Overdose

The possibility of an overdose of ^{177}Lu-PSMA-617 is unlikely, as the single-dose vial contains a predefined amount of radioactivity and is under the control of and administered by healthcare providers who are qualified by specific training and experience. No cases of overdose have been reported in the 2 prospective clinical studies PSMA-617-01 and PSMA-617-02 [SCS-Section-5.5].

^{177}Lu-PSMA-617 doses as high as 9.3 GBq have been administered in early phase dose-ranging clinical trials as known from literature, and no dose-limiting toxicities were observed (Rathke et al 2018). In the event of administration of a radiation overdose with ^{177}Lu-PSMA-617, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding, and the effective dose applied should be estimated.

5.4 Safety in special patient populations

The safety of ^{177}Lu-PSMA-617 was also evaluated across relevant patient subgroups including subgroups with and without AR pathway inhibitors at baseline, according to the numbers of cycles received, ECOG score at baseline, age, race, region, concurrent use of AR pathway inhibitors, concurrent use of radiation therapy, concurrent use of bone-sparing agents as part of BSC/BSoC treatment, baseline eGFR level, baseline proteinuria, baseline eGFR and proteinuria

levels, patients with renal impairment, presence of liver metastases at baseline, and baseline liver parameters.

Overall, the differences or trends observed in all these subgroup analyses (intrinsic factors [SCS-Section 5.1] or extrinsic factors [SCS-Section 5.2]) were as anticipated due to the medical nature of the factors analyzed, and did not raise any particular safety concerns.

In addition, AEs were also assessed in patients who received ≤4 cycles of ^{177}Lu-PSMA-617 and in those who received 5 or 6 cycles. Overall, there was no suggestion of a safety concern in patients who received more cycles, as discussed in [SCS-Section-5.2.3.1].

5.5 Adverse drug reactions

The identification and selection of drug-related adverse drug reactions after medical assessment is described in [SCS-Section 2.1.7], and the resulting aggregate list proposed for use in the prescribing information is shown in [SCS Appendix 1-Listing A1-1].

5.6 Safety conclusions

The safety profile of ^{177}Lu-PSMA-617 treatment, based on the results from the 2 prospective clinical studies (PSMA-617-01 and PSMA-617-02), was as anticipated given its mechanism of action, and is generally consistent with previous literature reports of ^{177}Lu-PSMA-617 in similar populations of patients with mCRPC (see Section 8).

The baseline characteristics of the patients with PSMA-positive mCRPC in these 2 studies reflect heavily pretreated patients with a high bone and visceral disease burden, which are important aspects to consider while assessing patient toxicities during treatment. Generally, the reported adverse events appeared to be predominantly grade 1 or 2 and most frequently reported as salivary gland, hematological, and gastrointestinal toxicities. While the grade ≥ 3 AEs were mainly restricted to hematological events, more adverse events were reported in patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (52.7%) vs. those receiving BSC/BSoC only (38.0%); however, the incidence of each grade ≥ 3 AE was low. The most frequent myelosuppression-related adverse events were anemia, thrombocytopenia, lymphopenia, leukopenia, and neutropenia, which may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions, but which may also be impacted by bone marrow impairment at baseline from prior therapy. The most frequent non-hematologic adverse events with ^{177}Lu-PSMA-617 treatment were fatigue, dry mouth, nausea, back pain, arthralgia, decreased appetite, constipation, vomiting, and diarrhea. Most of these (except dry mouth) were nonspecific and attributable to the administration of therapeutic levels of a radioactive compound. Overall, the data show that AEs were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. The safety of ^{177}Lu-PSMA-617+BSC/BSoC was also evaluated across relevant patient subgroups, and no unexpected differences were observed in any of the subgroups or between the two treatment arms.

Overall, a well-tolerated and manageable safety profile was demonstrated for ^{177}Lu-PSMA-617 in heavily pretreated patients with progressive PSMA-positive mCRPC.

6 Benefits and risks conclusions

6.1 Therapeutic context

6.1.1 Disease or condition

Prostate cancer (PC) is globally the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths in 2020 worldwide (Sung et al 2021). It is the second leading cause of cancer-related death among men in the USA, and the third leading cause in Europe (Malvezzi et al 2019, Siegel et al 2020). In the USA, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020), and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths (International Agency for Research on Cancer 2020).

Most patients with PC present with localized disease and undergo initial surgical and/or radiological therapy, with concomitant or subsequent use of ADT. Once metastasized, ADT is continued and is highly effective in eliciting a PSA response. However, the 5-year survival rate is 30% for patients who present with metastatic disease (American Cancer Society 2020), as the development of castration-resistance is inevitable, resulting in transition to the fatal mCRPC. Ten to twenty percent of patients with mPC become castration-resistant within 5 years and >50% die within 3 years with historical standard therapies (Nussbaum et al 2016). Once patients reach the mCRPC stage, their expected OS is low, as was seen in the randomized Phase III study of cabozantinib vs. prednisone in patients with mCRPC who had received prior docetaxel and abiraterone acetate and/or enzalutamide; the median OS of the prednisone control arm was 9.8 months (Smith et al 2016).

6.1.2 Current therapies

Docetaxel has been approved for patients with mCRPC for over 16 years, and during the past decade additional therapeutic options have been approved, including the taxane-based cytotoxic agent cabazitaxel, sipuleucel-T immunotherapy for asymptomatic or minimally symptomatic disease (currently withdrawn from use in the EU), the AR pathway inhibitors such as abiraterone acetate and enzalutamide, and the α-emitting bone-directed radiotherapy ^{223}Ra dichloride for bone-only metastases. More recently in patients with DDR mutations, PARP inhibitors have also been approved (e.g. olaparib) (de Bono et al 2020). A broader discussion of current therapies is provided in [SCE-Section-1.1.2].

While NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for the use of these treatments, there is no optimized sequence for delivery of these agents in patients with mCRPC. In clinical practice, the AR pathway inhibitors or docetaxel are often used in the first- or second-line mCRPC setting, resulting in a loss of activity in patients with later stage disease who have previously been exposed to these agents in the earlier stages of their disease (Tannock et al 2004, de Bono et al 2010, de Bono et al 2011, Scher et al 2012). Only one study has demonstrated efficacy after progression has occurred following treatment with these agents (Gillessen et al 2020).

Prolonged survival in this patient population is currently an unmet need and novel treatments are still required.

6.1.3 Unmet medical need

Despite the developments in treatment options described in Section 6.1.2, mCRPC still claims the lives of more than 375,000 men worldwide each year (Sung et al 2021). These patients, many of whom are elderly and frail, are often at risk of serious oncological complications making clinical management a significant challenge, especially since these patients have previously received treatment with many approved anticancer agents. A clinician's only therapeutic option is to administer BSC/BSoC or to cycle through previously used agents in hope of providing some palliative effect.

In addition, controlling bone disease is also important for these patients, since their median age at diagnosis of mCRPC is 70 years (Flaig et al 2016) and due to the disease's predilection for bone, approximately 90% of patients with mCRPC develop bone metastases, with 49% experiencing a serious SSE within 2 years (Saad et al 2004, Kirby et al 2011). Common presentations include bone pain, bone marrow failure, or complications such as pathological fractures and spinal cord compression. These occurrences typically require medical pain management with opioids, local radiation, or orthopedic surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005).

There is also a need for additional therapeutic options for prostate cancer progression in patients who are not medically suitable to receive taxanes (e.g., patients at risk of neuropathy), as information on real-world treatment patterns for men with mCRPC indicate that a majority do not receive taxane chemotherapy (George et al 2020). The phase III PSMA-617-01 study was designed to specifically select patients who had previously received taxanes to demonstrate that ^{177}Lu-PSMA-617 provides clinical benefit in patients that have tried all available treatments known to influence overall survival. However, mechanistically, there is no reason that the efficacy and safety of RLT with ^{177}Lu-PSMA-617 would be significantly altered in patients who have not previously received taxanes as compared to patients who have previously received taxanes (as were specifically selected for the phase III PSMA-617-01 study). As such, patients who are not medically suitable to receive taxanes for PSMA-positive mCRPC are still likely to derive clinical benefit from RLT with ^{177}Lu-PSMA-617. Thus, the clinical effectiveness and safety demonstrated in the phase III PSMA-617-01 study could be clinically and mechanistically extrapolated to encompass the unmet medical need in patients who would not be medically suitable to receive taxanes.

Given the limited treatment options following prostate cancer progression, there is a clear necessity for improved treatment regimens with a significant antitumor effect and minimal toxicity.

6.2 Benefits

Study PSMA-617-01 has shown that adding ^{177}Lu-PSMA-617 to BSC/BSoC consistently resulted in statistically significant improvements in key measures of efficacy, including a reduced risk of radiographic disease progression or death, a reduced risk of death, increased ORR and DCR, durable responses, and a delay in the time to first SSE. These benefits are summarized in Table 6-2, and are displayed graphically in Figure 6-1.

Results consistent with these benefits have been observed in other published clinical studies evaluating ^{177}Lu-PSMA-617 in the same population as in Study PSMA-617-01. These are discussed in detail in Section 8, with key efficacy results summarized in Table 1-4.

To evaluate the PSMA-617-01 data in the context of available therapies in the intended patient population, publications describing the use of approved agents for mCRPC in the third-line treatment setting are summarized in Table 6-1. Taken together, these published clinical studies demonstrate that treatment with ^{177}Lu-PSMA-617 induces PSA reduction and radiologic response that exceeds the antitumor activity of all currently approved agents being used as third-line treatment. Additionally, and within the limitations of this indirect cross-study comparison (given the differences in study designs, patient populations prior therapies and current treatments), an improvement in OS was also observed based on historical comparisons, where an OS of around 10 months was observed in patients who had exhausted all available therapies.

Table 6-1 Efficacy summary of approved agents and ^{177}Lu-PSMA-617 used as third-line treatment for mCRPC

Third-line treatment	# Patients	Patient-weighted averages			
		OS median (months)	≥50%[1] PSA Response (%)	PFS median (months)	ORR (by RECIST) (%)
Cabazitaxel[2]	594	12.3	32.3	4.5	21.6
Abiraterone acetate[3]	133	12.1	16.4	4.0	15.6
Enzalutamide[4]	696	9.7	19.4	3.5	9.3
Radium Ra-223 dichloride[5]	52	3.4[7]	-	-	-
Placebo (prednisone)[6]	346	9.8	2	-	-
VISION Prospective Study[8]					
^{177}Lu-PSMA-617 +BSC/BSoC	**551**	**15.3**	**46.0[9]**	**5.9[9]**	**29.8[10]/51.1[11]**
BSC/BSoC Only	280	11.3	7.1[9]	2.4[9]	1.7[10]/3.1[11]

[1] >50% response for enzalutamide, Thomsen et al (2014), Brasso et al (2015)

[2] Pezaro et al (2014), Sella et al (2014), Al Nakouzi et al (2015), Caffo et al (2015), van Soest et al (2015), Kongsted et al (2016), de Wit et al (2019), Hofman et al (2021)

[3] Loroit et al (2013), Noonan et al (2013), Caffo et al (2015)

[4] Badrising et al (2014), Schmid et al (2014), Thomsen et al (2014), Azad et al (2015), Brasso et al (2015), Caffo et al (2015), Cheng et al (2015), Badrising et al (2016), Davies et al (2016)

[5] Sidek et al (2018)

[6] Smith et al (2016)

[7] Mean

[8] Not patient-weighted averages

[9] PFS-FAS; ^{177}Lu-PSMA-617+BSC/BSoC (N = 385), BSC/BSoC only (N = 196)

[10] Response evaluable analysis set; ^{177}Lu-PSMA-617+BSC/BSoC (N = 319), BSC/BSoC only (N = 120)

[11] Response evaluable analysis set in patients with measurable disease at baseline; ^{177}Lu-PSMA-617+BSC/BSoC (N = 184), BSC/BSoC only (N = 64)

Analysis of the strengths, limitations and uncertainties of the evidence related to the key benefits

A notable strength for the key benefits is the consistency of a statistically significant effect across all endpoints, sensitivity analyses, and subgroups comprising enough patients for a meaningful comparison. These results were also consistent with other published clinical studies evaluating ^{177}Lu-PSMA-617 in the same population as in Study PSMA-617-01 (see Section 1.2.2)

It is acknowledged that there is limited data from Asian (2.4% of patients overall) or African American or Black (6.6%) patients from Study PSMA-617-01.

6.3 Risks

None of the safety observations from the safety evidence presented in Section 5 were considered to significantly impact the benefit-risk balance for treatment with ^{177}Lu-PSMA-617.

The AE data indicate that ^{177}Lu-PSMA-617 treatment has a well-tolerated and manageable safety profile in the intended patient population. Many of the more frequently reported adverse events are often observed in this patient population and may be related to the underlying disease and/or other comorbidities. The data show that these events were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. Causes of death were consistent with what would be expected in a population of patients with progressive PSMA-positive mCRPC. However, three risks were identified (summarized in Table 6-2, and are displayed graphically in Figure 6-1):

- **Myelosuppression**: based on the sensitivity of the bone marrow to radiation effects, this is considered a known risk for ^{177}Lu-PSMA-617, and data from the PSMA-617-01 sub-study showed that the mean absorbed radiation dose for ^{177}Lu-PSMA-617 in the red marrow was 0.035±0.020 Gy/GBq [SCP-Section 3.3.2]. The frequency of myelosuppression-related events (including anemia, thrombocytopenia, lymphopenia, leukopenia, neutropenia) was higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm (47.4% of patients) compared with the BSC/BSoC only arm (17.6% of patients). These events are discussed in detail in [SCS-Section-2.1.5.1]. The most frequent myelosuppression-related adverse events were anemia, thrombocytopenia, lymphopenia, leukopenia and neutropenia, but were considered manageable with standard clinical interventions.
- **Renal toxicity**: due to PSMA expression in the proximal tubule, and the known renal route of ^{177}Lu-PSMA-617 excretion, this is also considered a known risk for ^{177}Lu-PSMA-617, and data from the PSMA-617-01 sub-study showed that the mean radiation absorbed dose for the kidneys was 0.43 ± 0.16 Gy/GBq [SCP-Section 3.3.2]. Renal events were only observed in 8.7% of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and in 5.9% of patients in the BSC/BSoC only arm. These events are discussed in detail in [SCS-Section-2.1.5.1]. Overall, despite higher radiation exposures that may occur in the kidneys of patients treated with ^{177}Lu-PSMA-617, renal toxicity was predominantly low grade comprising creatinine increases that were manageable and reversible.
- **Grade ≥ 3 AEs**: while these adverse events were mainly restricted to hematological events, more adverse events were observed in patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (52.7%) vs. 38.0% of patients receiving BSC/BSoC only; however, the

incidence of each individual grade ≥ 3 AE was low. These events are discussed in detail in [SCS-Section-2.1.1].

Overall, limited and manageable safety-related risks were observed when adding ^{177}Lu-PSMA-617 to BSC/BSoC in heavily pretreated patients with progressive PSMA-positive mCRPC.

6.4 Benefit-risk assessment

Recommended use

The clinical safety review and detailed analyses of the radiation exposure support the intended dose and frequency of ^{177}Lu-PSMA-617 administration every 6 weeks (± 1 week) for a total of 6 cycles (doses) of 7.4 GBq, to deliver a total cumulative dose of 44.4 GBq.

Overall benefit-risk balance

The prevalence of mCRPC is increasing steadily, indicating that these patients have an urgent need for new, more effective treatment options that delay disease progression or prolong survival with acceptable toxicity and quality of life (Scher et al 2015).

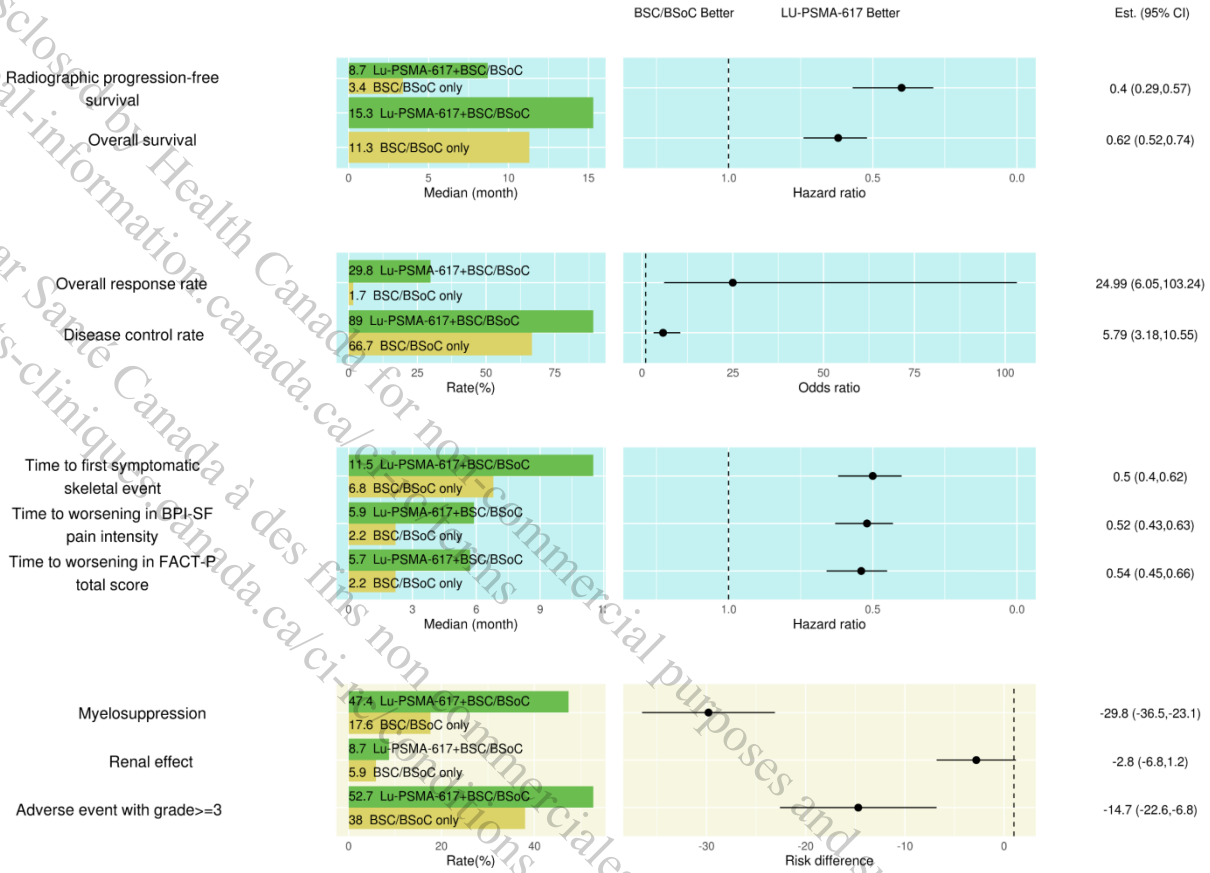
Study PSMA-617-01 is the first international, randomized study to demonstrate the ability of PSMA-targeted RLT to extend survival in mCRPC, establishing ^{177}Lu-PSMA-617 RLT as a new, effective and tolerable therapeutic option for patients with PSMA-positive mCRPC.

As shown in Table 6-2 and Figure 6-1, the addition of ^{177}Lu-PSMA-617 to BSC/BSoC in these patients led to statistically significant benefits with a well-tolerated and manageable safety profile that was generally consistent with previously published clinical study results.

Table 6-2 Key benefits and key risks of treatment with ^{177}Lu-PSMA-617+ BSC/BSoC

Key benefits: Adding ^{177}Lu-PSMA-617 to BSC/BSoC in heavily pretreated PSMA positive patients with progressive mCRPC results in the following statistically significant and clinically important benefits:		
rPFS	An estimated 60% reduction in the risk of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57; log-rank 1-sided p-value < 0.001)	A median rPFS prolongation of 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
OS	An estimated 38% reduction in the risk of death (HR = 0.62; 95% CI: 0.52, 0.74; log-rank 1-sided p-value < 0.001)	A median OS prolongation of 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
ORR	A 29.8% ORR in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 1.7% in the BSC/BSoC only arm, with an odds ratio of 24.99 (95% CI: 6.05, 103.24). The response was durable in the ^{177}Lu-PSMA-617+BSC/BSoC arm: median of 9.8 months (95% CI: 9.1, 11.7)	
DCR	A 89.0% DCR in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm, with an odds ratio of 5.79 (95% CI: 3.18, 10.55)	
Time to SSE	An estimated 50% reduction in the risk of a SSE or death (HR = 0.50; 95% CI: 0.40, 0.62)	The median time to SSE was delayed by 4.7 months, from 6.8 months (95% CI: 5.2, 8.5) in the BSC/BSoC only arm to 11.5 months (95% CI: 10.3, 13.2) in the ^{177}Lu-PSMA-617+BSC/BSoC arm
PRO FACT-P	FACT-P total score showed an estimated 46% risk reduction in worsening from baseline, clinical progression, or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm	There was a delayed time to worsening of the FACT-P total score with a median time of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm.
PRO BPI-SF	Delayed time to worsening of the BPI-SF pain intensity score, with less pain and less interference with daily activities	
	For the BPI-SF pain intensity scale: there was an estimated 48% reduction in risk of worsening, clinical progression or death (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm	For the BPI-SF pain interference scale: there was an estimated 43% reduction in risk of worsening, clinical progression or death (HR = 0.57; 95% CI: 0.47, 0.69; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm
Key risks: Limited safety-related risks were identified when adding ^{177}Lu-PSMA-617 to BSC/BSoC in heavily pretreated patients with progressive PSMA-positive with mCRPC:		
Myelosuppression	Adverse events associated with myelosuppression were observed in more patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (47.4%) vs. in 17.6% of patients receiving BSC/BSoC only	
Renal toxicity	Adverse events associated with renal toxicity were observed in more patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (8.7%) vs. in 5.9% of patients receiving BSC/BSoC only	
Grade ≥ 3 adverse events	While the grade ≥ 3 adverse events were mainly restricted to hematological events, more adverse events were observed in patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (52.7%) vs. in 38.0% of patients receiving BSC/BSoC only. In both treatment arms, individual AE preferred terms ≥ grade 3 were infrequently reported, except for anemia, thrombocytopenia, lymphopenia and fatigue, which are expected for ^{177}Lu-PSMA-617	

Figure 6-1 Benefit-risk diagram



Source: [Study PSMA-617-01-Table 14.2.2.1, Table 14.2.1.1, Table 14.2.3.1, Table 14.2.4.1, Table 14.2.9.1.2, Table 14.2.8.1.2, Table 14.3.3.4.2, Table 14.3.3.4.2, Table 14.3.2.3.1]

In conclusion:

- ^{177}Lu-PSMA-617 in combination with BSC/BSoC demonstrated statistically significant and clinically relevant improvements in OS and rPFS relative to BSC/BSoC alone. All key secondary endpoints, ORR, DCR and time to SSE were statistically significantly in favor of ^{177}Lu-PSMA-617+BSC/BSoC. In addition, improvements in PFS and biochemical responses and PRO results are consistent with the observed efficacy of ^{177}Lu-PSMA-617. These results were consistent with other published clinical studies for ^{177}Lu-PSMA-617 in this patient population.
- Safety in patients with mCRPC has been well characterized. ^{177}Lu-PSMA-617 is associated with a well-tolerated and manageable safety profile. AEs were often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. While many of the AEs reported may have an impact on QoL, it is important to note that QoL was not adversely impacted in patients treated with ^{177}Lu-PSMA-617 in addition to BSC/BSoC.

- The proposed labeling fully characterizes both efficacy and safety to enable the appropriate and safe use of ^{177}Lu-PSMA-617 in addition to BSC/BSoC to maximize therapeutic benefit while minimizing risk to patients. The data provided in this application and the full characterization of these data in the label support the safe and effective use of ^{177}Lu-PSMA-617 in addition to BSC/BSoC in the proposed indicated population of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy or who are not medically suitable for taxanes.

Taken together, the benefits of ^{177}Lu-PSMA-617 treatment outweigh the risks for its intended use intravenously every 6 weeks (± 1 week) for a total of 6 cycles (doses) of 7.4 GBq in patients with PSMA-positive mCRPC. ^{177}Lu-PSMA-617 meets an important unmet medical need in this patient population, with a well-tolerated and manageable safety profile.

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7.2 Minutes of Health Authority meetings

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7.3 Health Authority guidance

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8 Appendix: Summary of relevant publications

The following sections describe key results from published studies relevant to this application. However, it should be noted that neither Endocyte, AAA nor Novartis were involved in the clinical conduct of these studies.

Prospective, open-label, single-arm, non-randomized Phase II study (Violet et al 2020)

Violet et al (2020): a prospective, investigator-initiated, single-institution, single-arm Phase II study, comprising 50 patients with PSMA-positive mCRPC who progressed standard therapies, including antiandrogen therapies (abiraterone, enzalutamide or both) and taxane based chemotherapy (docetaxel or cabazitaxel), or who were not eligible for chemotherapy.

Median age was 71 years with 84% of patients having an ECOG performance status score of 0 or 1. A total of 84% had been exposed to docetaxel, 48% to cabazitaxel and 92% to abiraterone or enzalutamide or both. All patients underwent imaging with both ^{68}Ga-PSMA-11 (PSMA PET) and ^{18}F-FDG PET/CT (FDG PET). Inclusion mandated PSMA intensity at sites of disease to be significantly greater than normal (i.e., non-tumor) liver parenchyma, defined by SUVmax of tumor involvement of at least 1.5 × SUVmean of liver. Patients were excluded if FDG PET demonstrated major discordant disease, i.e. sites of FDG-positive and PSMA-negative disease, which were anticipated to be less likely to respond to therapy.

Patients received a mean dose of 7.5 (range: 4.0-8.9) GBq ^{177}Lu-PSMA-617 for 1-4 cycles every 6 weeks. The mean cumulative activity was 24.7 GBq, and the median number of cycles received was 4 (range: 1-4). Twenty-one patients received fewer than 4 cycles due to progressive disease during therapy (n = 10), an exceptional response to therapy (n = 8), prolonged cytopenias (n = 2), and non-cancer-related death (n = 1).

Adverse prognostic features of the cohort included short median PSA doubling time (2.3 months) and extensive prior treatment including prior docetaxel (84%), cabazitaxel (48%), and abiraterone and/or enzalutamide (92%). The primary endpoint was PSA response according to PCWG2 criteria defined as ≥50% PSA decline from baseline and toxicity according to CTCAE. Additional primary endpoints were imaging responses (as measured by bone scan, CT, PSMA PET, and FDG PET) and quality of life (assessed with the EORTC-QLQ-C30 and BPI questionnaires), all measured up to 3 months post completion of treatment.

PSA decline ≥ 50% was achieved in 32 of 50 patients (64%, 95% CI: 50, 77) (Table 1-3), including 22 patients (44%, 95% CI: 30, 59) with ≥ 80% decrease. Of 27 patients with measurable soft tissue disease, 15 (56%) achieved an ORR as defined by RECIST v1.1. Median OS as measured from date of enrollment was 13.3 months (95% CI: 10.5, 18.7) and median PSA PFS was 6.9 months (95% CI: 6.0, 8.7) (Table 1-4).

The study authors noted limited toxicity with improvements in pain and well-being. The most common toxicities attributed to ^{177}Lu-PSMA-617 were self-limiting CTCAE grade 1-2 dry mouth (66%), transient grade 1-2 nausea (48%), grade 1-2 fatigue (36%), and grade 1-2 vomiting (26%). Grade 3-4 toxicities were infrequent with lymphopenia (32%), thrombocytopenia (10%), anemia (10%), neutropenia (6%), and fatigue (2%). Grade 4 toxicity was limited to a single case of thrombocytopenia. Grade 1-2 renal injury occurred in 10% of patients; in 28 patients who had ^{51}Cr-EDTA measured before and 3 months after completion of ^{177}Lu-PSMA-617, there was a mean decline of 11.7 mL/min (95% CI: -19, -4).

Quality-of-life evaluations which included the EORTC-QLQ-C30 and BPI. Assessments were available for 79% of time-points. Overall, global health status improved on the EORTC QLQ-C30 by Cycles 2 and 3, with an increase of 6 and 7, respectively (95% CI: 0, 11 and 1, 13; p = 0.04 and 0.03, respectively); at the 3-month follow-up, this was stable compared to baseline. Overall, BPI pain severity and interference scores decreased at all time-points including at the 3-month follow-up with a decrease of -1.2 (95% CI: -0.5, -1.9; p = 0.001) and -1.0 (95% CI: -0.2, -1.8; p = 0.013), respectively. The pain scale on the EORTC-QLQ-C30 was also improved, concordant with the BPI findings.

Prospective, open-label, single-arm, non-randomized Phase II pilot study (Emmett et al 2019)

Emmett et al (2019): this prospective Phase II pilot study enrolled 14 patients with PSMA-positive mCRPC who progressed after abiraterone or enzalutamide and taxane-based chemotherapy (docetaxel and cabazitaxel) or were not eligible for chemotherapy.

All patients underwent screening imaging with ^{18}F-FDG and ^{68}Ga-PSMA-11 PET/CT scans, in addition to staging bone scan and CT of chest, abdomen, and pelvis. Patients received between 6.0 and 8.0 GBq ^{177}Lu-PSMA-617 for each treatment cycle on the basis of a combination of estimated glomerular filtration rate, patient weight, and number of sites of metastatic disease. Each treatment was undertaken a minimum of 6 weeks apart.

Median age was 69.5 years with 100% of patients having an ECOG performance status score of 0 or 1. A total of 64% had been exposed to docetaxel, 43% to 2 lines of chemotherapy, and 100% to either abiraterone or enzalutamide. The mean ^{177}Lu-PSMA-617 dose/cycle was 7.0 GBq.

Any PSA response to treatment was recorded in 10 (71%) of 14 patients, with a mean 59% reduction in PSA in those who experienced a treatment response. A reduction of ≥ 30% PSA was documented in 9 (64%) of 14 patients treated. A ≥ 50% reduction in PSA occurred in 5 patients (36%) (Table 1-3), of whom 4 out of 5 experienced a > 70% PSA reduction. Ten patients had measurable soft tissue at baseline; the ORR in measurable disease as defined by RECIST v1.1 was 40% (CR+PR). Mean OS was 50 ± 33 weeks (56 ± 38 weeks in patients with response vs. 36 ± 8 weeks in patients without response) (Table 1-4).

The most common toxicities were grade 1 dry mouth (78%), grade 1-2 nausea (71%), grade 1-2 fatigue (50%), grade 1 abnormal liver function tests (21%), and grade 1 diarrhea (14%). There were no grade 3-4 toxicities. All hematologic events were related to clinically significant disease progression for which the patient was removed from the study.

Prospective, open-label, stratified, two-arm, multicenter randomized Phase II study (TheraP; Hofman et al 2021)

Hofman et al (2021): this prospective, multicenter, open-label, randomized Phase II study (TheraP) enrolled 200 patients with PSMA-positive mCRPC who had prior docetaxel chemotherapy and were permitted to have abiraterone or enzalutamide. Patients were enrolled to one of two arms, stratified by disease burden (> 20 sites vs. ≤ 20 sites as measured on ^{68}Ga-PSMA-11 PET/CT), prior enzalutamide or abiraterone treatment, and study site.

Patients were randomized in a 1:1 ratio to receive either ^{177}Lu-PSMA-617 or cabazitaxel. The standard treatment group was cabazitaxel, given i.v. every 21 days at a dose of 20 mg/m^2, for up to a maximum of 10 cycles. Prednisolone 10 mg orally daily was administered throughout treatment with cabazitaxel. The experimental treatment group was ^{177}Lu-PSMA-617, administered by slow i.v. injection every 6 weeks. Treatment was administered for up to a maximum of 6 cycles. For each patient, the administered activity started at 8.5 GBq in Cycle 1, and was to be reduced by 0.5 GBq per cycle if there were no dose-limiting toxicities requiring an additional dose reduction. All patients underwent screening imaging with ^{18}F-FDG and ^{68}Ga-PSMA-11 PET/CT scans, in addition to staging bone scan and CT of chest, abdomen, and pelvis.

Two-hundred (200) of 291 screened patients were randomized to ^{177}Lu-PSMA-617 (N = 99) or cabazitaxel (N = 101). Seventeen patients withdrew or died before receiving study treatment (1 patient in the ^{177}Lu-PSMA-617 arm, and 16 in the cabazitaxel arm). All patients were treated with docetaxel prior to randomized treatment. In both arms, 91 patients (92% ^{177}Lu-PSMA-617 and 90% cabazitaxel) had also received either abiraterone or enzalutamide.

The primary endpoint of PSA response rate (decline ≥ 50%) was higher in those assigned ^{177}Lu-PSMA-617 than cabazitaxel (65/99 [66%; 95% CI: 56, 75] vs. 37/101 [37%; 95% CI: 27, 46]; $p < 0.0001$) (Table 1-4). At a median follow-up of 18.4 months, ^{177}Lu-PSMA-617 significantly improved PFS (HR = 0.63, 95% CI: 0.46, 0.86; $p = 0.0028$), rPFS (HR = 0.64, 95% CI: 0.46, 0.88; $p = 0.0070$), and PSA-PFS (HR = 0.60, 95% CI: 0.44, 0.83; $p = 0.0017$). Efficacy results were similar when analyses were restricted to the per-protocol population. OS data remain immature (90 deaths).

Grade 1-2 AEs occurred in 54% of ^{177}Lu-PSMA-617-treated patients vs. 40% of cabazitaxel-treated patients. Grade 3-4 AEs occurred in 33% of ^{177}Lu-PSMA-617-treated patients vs. 53% of cabazitaxel-treated patients. Grade 3-4 neutropenia was more common in the cabazitaxel arm (13%) as compared to the ^{177}Lu-PSMA-617 arm (4%). However, grade 3-4 thrombocytopenia was higher in the ^{177}Lu-PSMA-617 arm (11%) as compared to the cabazitaxel arm (0%). There were 6 grade 5 AEs for cabazitaxel and 13 grade 5 AEs for ^{177}Lu-PSMA-617 (none were treatment related). Discontinuations for toxicity occurred in 1/98 (1%) of ^{177}Lu-PSMA-617-treated vs. 3/85 (4%) cabazitaxel-treated patients.

Retrospective single-center study conducted in Germany (Rahbar et al 2018)

Rahbar et al (2018): 104 patients with mCRPC, who were treated with ^{177}Lu-PSMA-617 between December 2014 and December 2016, were included in this retrospective study.

PSMA imaging was performed in all patients using ^{68}Ga-PSMA-11 PET/CT or PET/MRI, according to institutional guidelines, to confirm PSMA expression in tumor lesions. The aim of

this study was to evaluate overall survival and parameters prognosticating longer survival in a large and homogeneous group of patients treated with ^{177}Lu-PSMA-617 radioligand therapy with heavily pretreated advanced mCRPC. Safety data was not presented in this retrospective study.

A total of 351 cycles of ^{177}Lu-PSMA-617 were applied in 104 patients. The median administered dose was 6.1 GBq (IQR 5.9–6.3) and the median cumulative injected activity in each patient was 18.8 GBq (IQR 12.9–24.75). A median of three cycles of ^{177}Lu-PSMA-617 were administered (range one to eight cycles). The majority of patients (97%) presented with bone metastases, 77% with lymph node metastases and 32% with visceral metastases. All patients were treated with at least one line of chemotherapy (docetaxel only or docetaxel and cabazitaxel) prior to ^{177}Lu-PSMA-617. Either abiraterone or enzalutamide had been given in 100% of the patients. Abiraterone was given in 80% of the patients and enzalutamide in 82% of the patients. Both AR pathway inhibitors (enzalutamide and abiraterone) had been given in 61% of the patients.

Follow-up data after the first cycle of ^{177}Lu-PSMA-617 RLT concerning PSA response was available for all patients. Any PSA decline occurred in 70 (67%) patients and a PSA decline ≥ 50% in 34 (33%) patients after the first cycle prior to receiving further therapy cycles (Table 1-3). For the entire cohort, the Kaplan-Meier analysis showed a median OS of 56.0 weeks (95% CI: 50.5-61.5) (Table 1-4). Univariate analysis of OS showed a noticeable longer median OS of 62.9 weeks (95% CI: 51.5, 74.3) in patients with any PSA decline than in patients with PSA progression (47 weeks; 95% CI: 39.5, 54.6; log-rank p=0.004) with a hazard ratio of 0.38 (95% CI: 0.19, 0.67, p=0.005). A comparison between patients with a PSA decline ≥ 50% and <50% did not show a significant difference concerning OS (log rank p=0.1). However, stepwise analysis of the percentage of PSA decline after the first cycle as a prognosticator of OS, a PSA decline ≥ 20.87% was determined as the best cut-point with a median OS of 68 weeks (95% CI: 57.9, 78.1) vs. 44 weeks (95% CI: 38.5, 49.5) and a hazard ratio of 0.28 (95% CI: 0.15, 0.51). Adjusting for the fact that several cut-points were tested, the upper bound of the p-value for the comparison of the two groups was 0.015. Cumulative injected activity ≥ 18.8 GBq and baseline ALP levels <220 U/L were also associated with a longer OS.

Retrospective single-center study conducted in Netherlands (van Kalmthout et al 2019)

van Kalmthout et al (2019): 30 patients with mCRPC who underwent ^{177}Lu-PSMA-617 treatment during the period of December 2016-September 2018 were included in this retrospective study.

Criteria for treatment in this study included confirmed histological diagnosis of PC and metastatic malignancy with no alternative cytotoxic treatment options; 1 or more previous treatments with chemotherapy, hormonal therapy, and either enzalutamide or abiraterone and/or inadequacy to undergo chemotherapy/hormonal therapy; World Health Organization performance status 2 or less; sufficient bone marrow capacity, sufficient renal function, baseline ^{68}Ga-PSMA PET/CT of 2 months or less prior to administration of the first therapy cycle; and metastatic disease with dominant tumor sites showing relatively high PSMA expression on baseline ^{68}Ga-PSMA PET/CT. The aim of the study was to summarize first experiences with ^{177}Lu-PSMA-617 at their institution by looking at PSA response via PCWG3,

clinical response via severity of pain and usage of analgesics after separate treatment cycles and clinical toxicity via CTCAE V4.03 criteria.

Median age was 70 years (range, 54–83 years) and a total of 67% had been exposed to docetaxel or cabazitaxel, 47% to abiraterone, and 73% to enzalutamide. Patients underwent 1 to 6 cycles with ^{177}Lu-PSMA; median number of cycles was 4. Mean administered radioactivity was 6 GBq (range, 5.6–6.4 GBq) per cycle. Median interval between therapy cycles was 6 weeks (range, 5.5–35 weeks). Median duration of follow-up from start of the first therapy cycle was 10 months (range, 1 week to 21 months).

Median PSA level at baseline was 200 ng/mL (range, 4.3–3800.0 ng/mL). During treatment, PSA level decreased 50% or greater in 57% of the patients (Table 1-3); PSA decrease of 90% or greater was observed in 24% of the patients. Notably, all biochemically stable patients (n=4) after the first cycle became biochemical responders after the second cycle. Of the 7 patients who were biochemically progressive after the first cycle, only 1 patient showed a secondary decrease and became stable after the second cycle. Prostate-specific antigen level of 2 other patients, however, increased after an initial PSA decrease of greater than 60%. During a median follow-up length of 13.7 months (range, 9.8–32.3 months), median overall survival from start of the first therapy cycle was 11.3 months (range, 1.4–32.3 months).

After the first cycle, a decreased usage of analgesics was seen in 9 of 20 evaluable patients (45%) who experienced pain at baseline. After 2 and 4 cycles, usage of analgesics decreased in 8 of 15 (52%) and in 6 of 8 evaluable patients (75%), respectively. In all 3 patients (100%) who suffered from pain at baseline and who were treated with 6 cycles, the pain symptoms were ameliorated during 6 therapeutic cycles.

During all treatment cycles evaluating clinical toxicity, newly originated fatigue was reported in 36% of the patients and remained limited to Grades 1/2. Xerostomia occurred in 47% of the patients limited to Grade 1/2. Generally, severity of baseline clinical symptoms did not deteriorate during the treatment cycles. A total of 8 CTCAE ≥ Grade 3 events were reported during the follow-up period, including (1) abdominal soft tissue swelling causing deep venous thrombosis and hydronephrosis, (2) papilledema causing visual deficit, (3) ileus, (4) pneumonia causing sepsis and cardiac decompensation, (5) paraplegia, (6) stroke, (7) carcinomatous peritonitis causing ascites and sepsis, and (8) hematuria. For all medical complications, intervention and/or hospital admission was required. During all treatment cycles evaluating biochemical toxicity, newly originated Grade 1 anemia occurred in 17% of the patients; Grades 2, 3, and 4 occurred in 7%, 3%, and 3%, respectively. New leukocytopenia was limited to Grade 1 and occurred in 20% of the patients. New Grades 1 and 2 thrombocytopenia occurred in 14% and 3% of the patients, respectively, whereas new Grades 1 and 2 renal insufficiency occurred in 10% and 3% of the patients. The authors note that in general, ^{177}Lu-PSMA-617 therapy was well-tolerated with a mild toxicity profile (predominantly CTCAE Grades 1/2) that was self-limiting and/or easily treated.

Retrospective single-center study conducted in Turkey (Demirci et al 2017)

Demirci et al (2017): 43 patients with mCRPC who underwent ^{177}Lu-PSMA-617 treatment during the period of 2014-2017 were included in this retrospective study.

Inclusion criteria included patients with castration-resistant prostate cancer who had progressed on abiraterone and progressed on docetaxel (or were contraindicated). Patients were required to be ECOG performance status 0-2 and demonstrate high uptake on PSMA PET/CT imaging. All patients had received prior abiraterone and 42 (98%) patients had received a prior taxane-containing regimen. A total of 91% of patients had bone metastases, 56% had lymph node metastases and 19% had visceral metastases.

A total of 60.5% of patients received 4 treatments, 18.6% received 3 treatments, and 20.9% received 2 treatments. The median cumulative dose was 21 (±7.2) GBq.

The average PSA level at baseline was 264 ± 108 ng/mL. A reduction of more than 50% in PSA levels was observed in 53% of patients (Table 1-3). Among 28 patients who had a follow-up ^{68}Ga-PSMA PET/CT, 12 patients (27.9%) had progression, and 16 patients (57.1%) had partial response. The median Kaplan-Meier survival estimate was 15.0 months (95% CI: 12.2, 17.8). Progression was based on combined evaluation of PSA levels and available imaging modalities. Estimated median PFS was 6.5 months (95% CI: 4.0, 8.9). For patients with a reduction of more than 50% in PSA level, PFS was 17.7 months (95% CI: 14.3, 21.1). For patients with increased PSA levels, PFS was 13.8 months (95% CI: 10.1, 17.6). The prolongation in OS was statistically significant ($p<0.05$).

Hematotoxicity by SWOG criteria was reported in 9 patients (20.9%) with Grade 1 toxicity, 2 patients (4.7%) with Grade 2 toxicity, and 3 patients (7%) with Grade 3 toxicity. There was no Grade 3-4 nephrotoxicity.