



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMADOC-1700519818-2327249
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000288073

Invented name: Pluvicto

International non-proprietary name: lutetium (^{177}Lu) vipivotide tetraxetan

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to PRAC/CHMP members.

Status of this report and steps taken for the assessment				
Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
☐	Submission deadline	30 Jul 2025	25 Jul 2025	☐
☐	Validation	15 Aug 2025	29 Jul 2025	☐
☐	Start date	16 Aug 2025	16 Aug 2025	☐
☐	CHMP (Co-) Rapporteur AR	10 Oct 2025	10 Oct 2025	☐
☐	PRAC Rapporteur AR	17 Oct 2025	28 Oct 2025	☐
☐	Co-Rapporteur assessment	22 Oct 2025	22 Oct 2025	☐
☐	PRAC comments	22 Oct 2025	22 Oct 2025	☐
☐	Updated PRAC Rapporteur AR	23 Oct 2025	23 Oct 2025	☐
☐	PRAC outcome	30 Oct 2025	30 Oct 2025	☐
☐	CHMP comments	3 Nov 2025	3 Nov 2025	☐
☐	Updated CHMP Rapporteur AR	6 Nov 2025	7 Nov 2025	☐
☒	Request for supplementary information	13 Nov 2025	13 Nov 2025	☐

¹ Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

² Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

³ Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Procedure resources	
Rapporteur:	Janet Koenig

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List of abbreviations used in the text

AAA	Advanced Accelerator Applications
AAA617	lutetium (177Lu) vipivotide tetraxetan
ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
ARPI/ARDT	Androgen receptor pathway inhibitor
BICR	Blinded independent central review
BOR	Best overall response
BPI-SF	Brief pain inventory-short form
BSC	Best Supportive Care
CAS	Crossover Analysis Set
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Complete response
CRPC	Castration-resistant prostate cancer
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
ECA	External control arm
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-dimension, 5-level
FACT-P	Functional assessment of cancer therapy – prostate
FDA	Food and Drug Administration
FAS	Full analysis set
Ga-FAS	Ga-PSMA-11 full analysis set
GBq	Gigabecquerel
HR	Hazard ratio
HRQoL	Health-related quality of life
HSPC	Hormone-sensitive prostate cancer
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IRT	Interactive response technology
IV	Intravenous
LDH	Lactate dehydrogenase
K-M	Kaplan-Meier
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
NCCN	National 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
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PR	Partial response
PROs	Patient reported outcomes
PSA	Prostate specific antigen

PSMA	Prostate-specific membrane antigen
QoL	Quality of life
RAS	RECIST analysis set
RECIST	Response evaluation criteria in solid tumours
RLT	Radioligand therapy
RMST	Restricted mean survival time
rPFS	Radiographic progression-free survival
RPSFT	Rank preserving structural failure time
rwOS	Real-world overall survival
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SD	Stable disease
SSE	Symptomatic skeletal event
TCA	Trial control arm
TEAE	Treatment-emergent adverse event
TTA	Trial treatment arm
TTCT	Time to chemotherapy
TTPSAP	Time to PSA progression
TTSSE	Time to symptomatic skeletal event
TTSTP	Time to soft tissue progression
USA	United States of America
WoC	Withdrawal of consent

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 25 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) and for whom chemotherapy is not yet clinically indicated for PLUVICTO, based on interim results from study CAAA617B12302 (PSMAfore); this is a phase III, open-label, multi-center, randomised study comparing 177Lu-PSMA-617 vs. a change of androgen receptor-directed therapy in the treatment of taxane naïve men with progressive metastatic castrate resistant prostate cancer; As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted to include clinical data from the PSMAfore study to support the addition of the new therapeutic indication.

The requested variation(s) proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0127/2019) of 17 April 2019 on the granting of a product specific waiver for 177Lu-PSMA-617 (EMA-002419-PIP02-18) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

GLP/GCP inspections

No non-clinical/clinical study sites were inspected in connection to this variation.

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) and for whom chemotherapy is not yet clinically indicated for PLUVICTO, based on interim results from study CAAA617B12302 (PSMAfore); this is a phase III, open-label, multi-center, randomised study comparing 177Lu-PSMA-617 vs. a change of androgen receptor-directed therapy in the treatment of taxane naïve men with progressive metastatic castrate resistant prostate cancer; As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted to include clinical data from the PSMAfore study to support the addition of the new therapeutic indication.

☐ is recommended for approval.

☐ is not recommended for approval.

☒ is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be^{1 2}:

- ☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)
- ☒ 60 days (36 days to assess)

2. Introduction

2.1. Problem statement

Disease or condition

Pluvicto (AAA617, AAA617B1/lutetium (¹⁷⁷Lu) vipivotide tetraxetan) is a radioligand therapeutic product which was approved in the EU based on the results of the pivotal phase III Study PSMA-617-01 (VISION trial) for the indication (3L):

In combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane-based chemotherapy.

¹ Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.

² Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

Now the MAH applies for Pluvicto an extension of indication for an earlier treatment line in this disease with the proposed wording:

“treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI) and for whom chemotherapy is not yet clinically indicated.

This claim is based on the results from one pivotal study, namely study CAAA617B12302 (PSMAfore trial).

Epidemiology and risk factors, screening tools/prevention

Prostate cancer is the third leading cause of cancer-related deaths among men in Europe (Malvezzi et al 2023, Siegel et al 2024). In Europe, 473,011 new cases and 115,182 deaths were estimated for 2022 (International Agency for Research on Cancer 2022).

Clinical presentation, diagnosis, and stage/prognosis

Most patients with prostate cancer present with localised disease and undergo initial surgical and/or radiation therapy, with concomitant or subsequent use of androgen deprivation therapy (ADT) and other treatments. Prostate cancer patients who develop metastasis after treatment of localised disease, and patients who present with de novo metastatic disease inevitably develop castration resistance, resulting in transition from metastatic hormone sensitive prostate cancer (mHSPC) to mCRPC. ARPI/ARDTs can be highly effective in eliciting a therapeutic response.

However, the majority of mCRPC patients suffer morbidity from their disease including bone metastases and symptomatic (e.g. pain) and/or serious skeletal events (e.g. fractures) that significantly affect quality of life and shorten median overall survival (OS), which remains ≤ 2 years (Bubendorf et al 2000; Marques et al 2010; McKay et al 2017; Liu et al 2020; Freedland et al 2023; Schaeffer et al 2023).

Although the therapeutic landscape of mCRPC has broadened over the last decade, there is still a need to develop new treatment options, as patients with mCRPC have a poor prognosis and survival rates of less than 50% within 3 years (Freedland et al 2023, Nussbaum et al 2016), with an OS that becomes shorter with each successive line of treatment (Smith et al 2016, Shore et al 2021).

The intent of Study B12302 was to demonstrate that AAA617 provides an alternative treatment with mechanistic switch and meaningfully improved outcomes for mCRPC patients after first progression on ARPI/ARDT.

Management

Recent drug approvals in prostate cancer have brought clinical benefit to subgroups of patients who were selected based on genetic alterations in DNA repair pathways (Antonarakis et al 2020, Abida et al 2020, de Bono et al 2020, Hussain et al 2020), however, only a minority of patients have tumours that harbour those molecular markers (Pritchard et al 2016, Chung et al 2019, Abida et al 2019).

By contrast, PSMA is expressed in >80% of men with prostate cancer leading to the development of PSMA-directed therapies (Bostwick et al 1998, Hope et al 2017, Hupe et al 2018, Pomykala et al 2020). PSMA-targeted RLT offers the possibility of treating the cancer lesions in a specific and tumour-selective manner by exploiting cell surface receptors that are highly expressed on malignant prostate cancer cells as compared to normal 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 prostate cancer cell leading to cell death by release of beta particle radiation (Benešová et al 2015).

AAA617 can selectively target prostate cancer cells while sparing most normal tissues in patients whose tumours express PSMA based on dedicated imaging (Rowe et al 2020). Based on the phase III Study PSMA-617-01 (also known as VISION), the AAA617 (Pluvicto) was approved in the EU for adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI/ARDT and taxane-based chemotherapy.

2.2. About the product

The active moiety of Pluvicto is the radionuclide lutetium-177 which is linked to a small-molecule ligand that targets and binds with high affinity to PSMA, a transmembrane protein that is highly expressed in prostate cancer, including mCRPC. Upon the binding of Pluvicto to PSMA-expressing cancer cells, the beta-minus emission from lutetium-177 delivers therapeutic radiation to the targeted cell, as well as to surrounding cells, and induces DNA damage which can lead to cell death. (Pluvicto SmPC 5.1)

The recommended treatment regimen of Pluvicto is 7 400 MBq intravenously every 6 weeks (± 1 week) for up to 6 doses. (Pluvicto SmPC 4.2)

2.3. The development programme/compliance with CHMP guidance/scientific advice

2.3.1. Consideration of study design, guidelines, and regulatory input

For the assessment of this application, it is important to consider the sequences of treatment lines in mCRPC as described in the scientific European EAU guideline for prostate cancer (updated March 2025): The majority of mCRPC patients present with bone metastases and may develop symptomatic (e.g. pain) and/or severe (e.g. fractures) serious skeletal events that significantly affect quality of life and shorten median overall survival (OS), which remains ≤ 2 years.

Patients with metastatic disease, presenting initially or after localized treatment, are managed according to the EAU guideline with ARDT as first line treatment.

ARDT, androgen deprivation therapy (ADT), and androgen receptor (AR) pathway inhibitors (ARPI) can be highly effective in eliciting a prostate specific antigen (PSA) response. However, the development of resistance to androgen suppression is inevitable, resulting in transition to metastatic castration-resistant prostate cancer and disease progression.

Thus, the EAU guideline recommends after progression on ADT/ARDT/ARPI treatment for the second line the use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence. The guideline emphasises that chemotherapy should be applied early enough when the patient is still fit for chemotherapy and not be delayed. This is supported by high-level evidence showing an increase in PFS and OS from chemotherapy in the second line mCRPC.

Moreover, the guideline clarified that a sequencing of androgen receptor targeted agents at this stage should be avoided.

Treatment beyond the second line ("patients with mCRPC and progression following docetaxel chemotherapy") is more complicated and heterogeneous due to the issue that the EAU guideline

recommends strongly that “the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, 177lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T, and for patients with DNA homologous recombination repair (HRR) alterations olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, talazoparib/enzalutamide).”

Thus, the use of Pluvicto (177Lu-PSMA-617) is currently recommended in the guideline in the third line for pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.

Now the MAH applies for the treatment of a less advanced population of mCRPC in an earlier treatment line, which is currently not established in the sequencing of treatment. The intended target population is mainly characterised by progression after first line ADT/ARDT/ARPI therapy and before any second-line taxane chemotherapy.

Since almost all patients with mCRPC will progress after first-line ARDT, it is likely that nearly all of them would receive AAA617 in the next step as second line treatment. Docetaxel-chemotherapy, will become delayed and third line treatment, although it remains unknown whether chemotherapy after AAA617 is still as beneficial as currently documented. This proposal is not in accordance with the current guideline recommendation

The applicant justifies this decision with the argument that “to provide *the mCRPC population with a high medical need an effective and well tolerated alternative option for patients who desire to defer or completely avoid chemotherapy after initial progression on ARPI.*

The intent of PSMAfore was to demonstrate that AAA617 provides an alternative treatment with mechanistic switch and meaningfully improved outcomes for mCRPC patients after first progression on ARPI. Other trials in chemotherapy-naïve mCRPC have likewise used ARPI switch included as comparator arm (CONTACT-02, TRITON3, and SPLASH), in recognition of this particular subpopulation with unmet need (de Bono et al 2020, Fizazi et al 2023, Agarwal et al 2024, Hansen et al 2025).

2.3.2. Regulatory input

Key Health Authority interactions specific to Study B12302 are summarized in [Table 1-3](#).

Table 1-3 Key HA interactions specific to Study B12302

Interaction Date	Objective	Outcome
FDA Type B End of phase II Meeting under IND 133661 25-Aug-2020	To seek guidance on the proposed development of AAA617 as a potential new therapy for mCRPC patients following progression on ARPI/ARDT. The Sponsor’s inquiries focused on the phase III study proposal, including study design, endpoints, population, dose, and statistical methodology	FDA provided preliminary comments on 18-Aug-2020 and the Sponsor subsequently canceled the meeting scheduled for 25-Aug-2020 due to all topics for discussion being addressed in writing. FDA comments were addressed in the protocol or in a response document provided by the Sponsor upon submission of the protocol to IND 133661.

FDA Type B Pre-Submission Meeting under IND 133661 06-Jan-2023	To seek alignment with the agency on the acceptability and content of a proposed sNDA to update the Pluvicto indication to treat patients with mCRPC who have been treated with ARPI/ARDT based on the primary analysis for PSMAfore.	FDA advised that the Sponsor should collect additional overall survival and safety data prior to submission of the sNDA. The Sponsor proposed the timing and statistical analysis plan for an additional IA at ~40% OS information fraction to which the FDA did not object. The Sponsor submitted the updated SAP to IND 133661 in March 2023 at which time FDA requested the IA be updated to be event driven. The Sponsor complied and submitted an updated SAP for an IA planned at ~125 OS events.
Interaction Date	Objective	Outcome
FDA Type B Pre-Submission Meeting under IND 133661 13-Sep-2023	To seek alignment with the agency on the acceptability and content of a proposed sNDA to update the Pluvicto indication to treat patients with mCRPC who have been treated with ARPI/ARDT based on IA2 for PSMAfore 2.	FDA advised that the Sponsor should collect additional overall survival data prior to submission of the sNDA.
2024 EMA SA	Scientific Advice provided for a different product of the applicant.	CHMP stated that "... it is known that the use of sequential ARPIs in mCRPC has showed limited benefit and that in chemotherapy-naïve patients the preferred choice after ARPI failure would be docetaxel (EAU guidelines). ... Therefore, the comparator in trial PSMAfore is not the current standard of care, and the results of this trial should not be used to support the use of [177Lu]Lu-PSMA-617 in taxane-naïve patients."
CHMP (Co-)Rapporteurs pre-submission meeting 15-May-2025	To obtain feedback from the CHMP Rapporteur and Co-Rapporteur on PSMAfore clinical data package to evaluate a new indication for Pluvicto®.	The Rapporteurs questioned the choice of comparator arm and the use of cross-over in the trial. They raised the importance of OS for the benefit/risk assessment of the therapy in this disease setting. They also recommended to clarify the relevance of the post-hoc analysis in the subgroup of asymptomatic or mildly symptomatic study participants.
Source: FDA (2020a) , FDA (2020b) , FDA (2023a) , FDA (2023b) , BfArM (2025)		

2.4. General comments on compliance with GCP

The MAH confirmed that Study B12302 was conducted in full compliance with current Good Clinical Practices and was closely monitored by Novartis personnel, or a contract research organization for compliance to the protocol, Novartis SOPs, and applicable regulatory guidance.

Assessment revealed no significant finding which would raise concerns against this statement.

3. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable for the applied extension of indication. However, with respect to the Ecotoxicity/environmental risk assessment the MAH is requested to note the following remark:

Off-note:

"The applicant refers to the ERA submitted during the initial marketing authorization. Although with this variation the indication is extended to a new patient population, the PEC was initially calculated with the default F_{pen} , therefore, the calculation is still acceptable.

Nevertheless, we would like to mention that in the meantime the guideline for the ERA of HMP was revised. The applicant even cites the revised GL but did not update the ERA accordingly.

Furthermore, we would like to refer to our assessment of the ERA during the initial marketing authorization. The applicant still cites the non-refined PEC and refers to a non-acceptable literature value for the $\log K_{ow}$. Both was commented by us in the past and is reflected in the EPAR of Pluvicto. "

These issues are acceptable for this variation, but they should be corrected in the ERA for any future variations.

4. Clinical aspects

4.1. Introduction

Since December 2022 Pluvicto is approved in the EU in the 3rd-line setting of mCRPC (detailed indication see above) ([EMA/H/C/005483](#)). The current procedure is an application for an extension of indication for an earlier-line treatment of mCRPC patients based on a single pivotal study, namely CAAA617B12302 (PSMAfore-Trial) ([NCT04689828](#)).

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies is provided below.

Pivotal trial

Study CAAA617B12302

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: CAAA617B12302 (PSMAfore) Countries:	Design, purpose & population: PSMAfore: A phase III, open-label, multi-center, randomised study comparing ¹⁷⁷ Lu-PSMA-617 vs. a change of androgen receptor-directed therapy in the treatment of taxane naive men with progressive metastatic castrate-resistant prostate cancer	Total: 468 (randomised) Age: 43-94 (71.4) years	Form(s): Radiopharmaceutical solution for infusion/injection: ¹⁷⁷ Lu-PSMA-617 (1 GBq/mL)	Study Status: ongoing; Primary analysis and final OS analysis complete
Austria, Belgium, Canada, Czech Republic, France, Germany, Netherlands, Poland, Slovakia, Spain, Sweden, Switzerland, United Kingdom, United States Start: 15-Jun-2021 End: 02-Oct-2022 (cut-off rPFS primary analysis); 27-Feb-2024 (cut-off 3 rd interim OS);		Groups: 2 234 234	⁶⁸ Ga-PSMA-11 (25 µg) – for screening Oral use ARPI/ARDT (abiraterone or enzalutamide) per local label Duration: Primary analysis: dosing every 6wks for 6 cycles (36wks) Long-term follow-up: until accrual of events for planned OS-based analysis Doses:	Report no. Study CAAA617B12302 Final CSR Report date: anticipated Q4-2026 Report no. [Study CAAA617B12302 IA3], full, final (v3.0) Report date: 11-Feb-2025 Report no. [Study CAAA617B12302 IA4], supplemental, final (v1.0) Report date: 31-Mar-2025 Report no. [Study

01-Jan-2025 (cut-off 4 th interim and final OS)			¹⁷⁷Lu-PSMA-617 7.4 GBq (±10%) ARPI/ARDT (abirateron e and enzalutami de) upon confirmation of rPD by BICR, participants were allowed to cross over to receive ¹⁷⁷Lu-PSMA-617 (36wks as above)	CAAA617B12302 CSR Addendum 1], supplemental, final (v1.0) Report date: 03- Jul-2025 Other reports: Study CAAA617B12302 Kidney and tumour dosimetry report (v2.0) Report date: 25-Mar-2025
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Supportive Trial

VISION (pivotal for the approved indication)

Protocol No., Countries & Study Dates	Study Design, Purpose & Population Studied	Total No., Age Range (mean), Group No.	Treatment, Route, Regimen, Duration of Therapy, Dosage	Study Status & Reports of Study Results
Protocol: PSMA-617-01 (VISION) Countries: Belgium, Canada, Denmark, France, Germany, Netherlands, Sweden, United Kingdom, United States Start: 29-May-2018 End: 27-Jan-2021 (cut-off primary analysis); 14- Dec-2023 (cut-off final analysis)	Design, purpose & population: An international, prospective, open-label, multicenter, randomised, phase 3 study of ¹⁷⁷Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)	Screening phase: 1003 patients received 68Ga-PSMA-11 Age: 40-94 (69.9) years Groups: 1 68Ga-PSMA-11 Treatment phase: 831 patients randomised to treatment with ¹⁷⁷Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC alone Age: 40-94 (70.0) years Groups: 2 Group 1: 551	Form(s): 68Ga-PSMA-11 (gallium (68Ga) gozetotide) single i.v. injection Dosing information: 111-185 MBq (3-5 mCi) Imaging time: PET 50-100 min p.i. Form(s): ¹⁷⁷Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan) i.v. administration Duration: Primary analysis: dosing every 6wks for up to 6 cycles (36wks) 38 months: treatment/assessment period	Study Status: complete Report no. [PSMA-617-01 primary analysis] full, final Report date: 28-Jun-2021 Report no. [PSMA-617-01 Final CSR] full, final (v2.0) Report date: 20-Sep-2024

			and long-term follow-up assessment Doses: 177Lu-PSMA-617 7.4 GBq (200 mCi) (±10%) + BSC for PC asdefined by the investigator	
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4.2. Biopharmaceutics, Pharmacokinetics and Pharmacodynamics

No biopharmaceutic, clinical pharmacology or pharmacodynamic studies were conducted or needed in support of this new indication Type II variation.

5. Clinical efficacy

5.1. Dose response study(ies)

Rationale for dose studied

The dose used in Study B12302 is the same that has been approved for AAA617 in the mCRPC population based on efficacy and safety results from Study PSMA-617-01 (VISION study). The recommended treatment regimen for AAA617 is 7.4 GBq (200 mCi) administered intravenously every 6 weeks for 6 cycles (doses). At the time of Study B12302 protocol development, the clinical experience with AAA617 in patients with mCRPC had been documented in numerous publications, summarizing the dosimetry, safety and efficacy at various doses and schedules [Study B12302 IA3-Appendix 16.1.1 Protocol-Section 4.2].

Preliminary results from Study TheraP (Hofman et al 2021) (6 to 8.5 GBq intravenously every 6 weeks up to 6 cycles) and Study PSMA-617-01 (VISION) (7.4 GBq intravenously every 6 weeks for up to 6 cycles) had demonstrated that AAA617 was well tolerated (Sartor et al 2021), which further supported the selected dose and frequency of AAA617 in Study B12302.

5.2. Main study Pivotal Trial: CAAA617B12302 (PSMAfore-Trial)

*Title of study: **PSMAfore**: A phase III, Open-label, Multi-Center, Randomised Study Comparing 177Lu-PSMA-617 vs. a Change of Androgen Receptor-Directed Therapy in the Treatment of Taxane Naïve Men with Progressive Metastatic Castrate Resistant Prostate Cancer*

EudraCT No. 2020-003969-19;

NCT04689828

5.2.1. Methods

Study B12302 is an open-label, multicenter, randomised study for PSMA-positive mCRPC patients previously treated with an ARPI/ARDT for whom it was considered appropriate to delay taxane-based chemotherapy.

The study evaluated the superiority of AAA617 over a change of ARPI/ARDT treatment in prolonging rPFS.

Only patients with PSMA-positive cancer were randomised in the study provided all other eligibility criteria were met. Enrolled patients were ≥ 18 years of age, had no prior taxane-containing regimen for progressive CRPC or hormone-sensitive prostate cancer (HSPC), and had a gallium (68Ga) gozetotide positron emission tomography (PET)/computed tomography (CT) scan assessed for eligibility by a central reader.

Patients had mCRPC and progressed only once on a prior second-generation ARPI/ARDT (abiraterone acetate, enzalutamide, darolutamide or apalutamide) as their most recent therapy.

Patients were randomised using a 1:1 ratio to receive either 7.4 GBq (200 mCi) $\pm$ 10% AAA617 once every 6 weeks (1 cycle) for 6 cycles or a change in ARPI/ARDT (abiraterone or enzalutamide).

Randomisation was stratified by 2 factors:

- Setting of prior ARPI/ARDT use: CRPC vs. HSPC

- Symptomatology based on item 3 of brief-pain inventory short form (BPI-SF) questionnaire: asymptomatic or mildly symptomatic (score of 0-3) vs. symptomatic (score >3)

The study consisted of a randomization period, treatment period, end of treatment (EOT) period, crossover period, and post-treatment follow-up period (includes 30-day safety follow-up). Participants who no longer agreed to follow-up assessments were followed for survival and AEs.

Study treatment began within 14 (+3) days after randomization. Participants received 7.4 GBq (200 mCi) $\pm$ 10% AAA617 once every 6 weeks for 6 cycles as per the schedule of assessments. Best supportive care, including ADT and palliative radiotherapy, was allowed.

For participants randomised to the ARPI/ARDT arm, the change of ARPI/ARDT treatment for each participant was selected by the treating physician prior to randomization and was administered per the physician's orders.

Best supportive care, including ADT and palliative radiotherapy, was allowed. After the last day of study treatment (treatment discontinuation for any reason) or upon radiographic progression as assessed by blinded centralized review, the participants must have an EOT visit performed $\leq$ 7 days and enter the Post-treatment Follow-up.

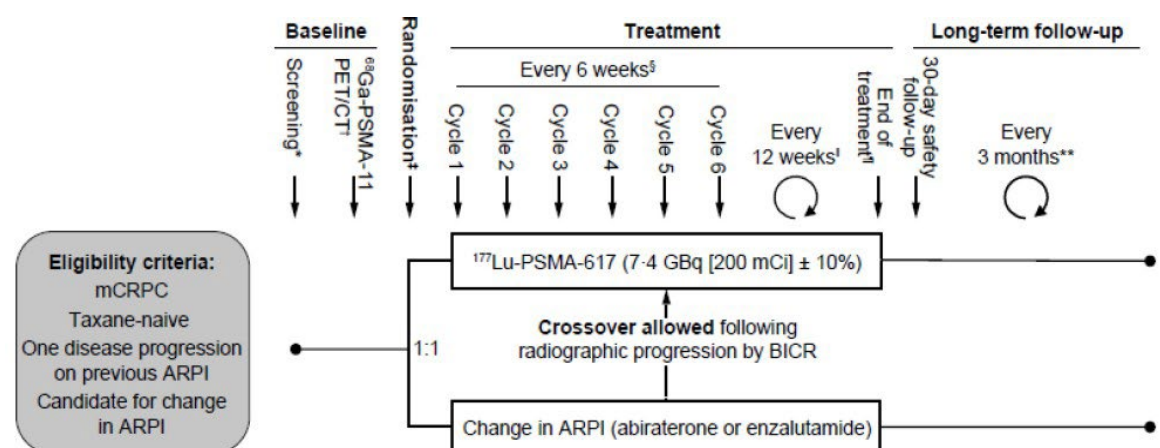
Upon confirmation of rPD by BICR, participants randomised to the ARPI/ARDT arm were allowed to either crossover to receive AAA617 or receive any other therapy per the discretion of the treating physician in the post-treatment follow-up period. Start of new intervening systemic antineoplastic therapies disqualified participants from crossing over. Other eligibility criteria for crossover included resolved prior treatment toxicity to baseline or Common Terminology Criteria for Adverse Event (CTCAE) grade 2, Eastern Cooperative Oncology Group (ECOG) status of 0-1, and adequate organ function.

Participants who received AAA617 and remain in follow-up on the study at the sponsor's completion of the study will be asked to join a separate study of long-term safety (CAAA617A12402) for a duration of up to 10 years.

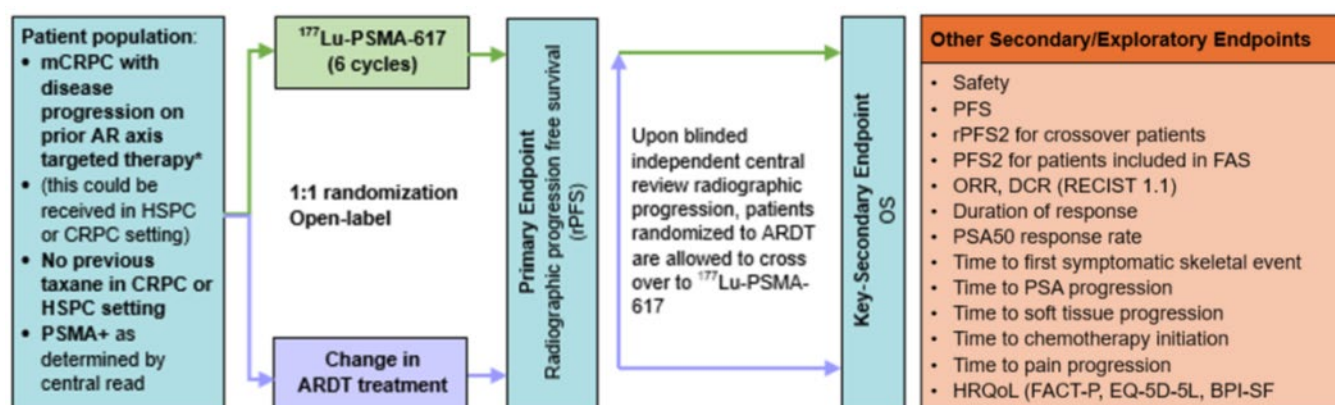
Participants who did not want to continue follow-up visits and assessments, but remained on study, were moved to survival follow-up where scheduled contact with the participant captured new antineoplastic therapies, adverse events (AEs) related to study treatment, safety topics of interest, and death.

The following Figure 1 provides an overview about the study design and the evaluation schedule:

Figure 1 Study design



CT/MRI and ^{99m} Tc bone scans	X††	... Every 8 weeks for 24 weeks, then every 12 weeks ...							X		X
ECOG performance status	X	X								X	X
HRQoL and pain scores‡‡	X§§	X	X	X	X	X	X	X	X	X	X
Physical examination™	X	X	X	X	X	X	X	X	X	X	X
Weight	X									X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Testosterone and PSA	X		X	X	X	X	X	X	X	X	X***
Haematology and biochemistry	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X†††



Stratification factor: Prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic vs symptomatic patients

* Candidates who are considered appropriate for delaying taxane-based chemotherapy

The following analysis sets were utilized for evaluation of efficacy in this study:

The **Full Analysis Set (FAS)** consisted of all patients to whom study treatment (AAA617 and ARPI/ARDT) had been assigned by randomisation. According to the ITT principle, patients were analyzed according to the treatment and strata they had been assigned to during the randomisation procedure. The FAS was the primary population for all efficacy analyses.

The **Crossover Analysis Set (CAS)** consisted of patients randomised to the ARPI/ARDT arm who crossed over after BICR-confirmed radiographic progression to receive at least one dose of AAA617. This analysis set was used for all analyses (rPFS2) pertaining to rPFS evaluations collected after patients crossed over into AAA617.

The **RECIST Analysis Set (RAS)** consisted of a subset of patients in the FAS with evaluable soft tissue disease by PCWG3-modified RECIST v1.1 defined as having at least one lesion (target or non-target) identified at baseline in soft tissue. Patients were to be included in the arm to which they were randomised. This analysis set was used for the analysis of RECIST-based endpoints (e.g., TTSTP, ORR, DOR, etc.).

The gallium (68Ga) gozetotide **FAS (Ga-FAS)** included all patients who received the administration of gallium (68Ga) gozetotide. This analysis set is the basis of safety and imaging summaries for the gallium (68Ga) gozetotide specific analyses. This included all screened patients who received gallium (68Ga) gozetotide and were randomised, and those who received gallium (68Ga) gozetotide but were not randomised.

5.2.2. Study participants

5.2.2.1. Diagnosis and main criteria for inclusion:

Adult PSMA-positive mCRPC male participants who were previously treated with an ARPI/ARDT and who were candidates for ARPI/ARDT switch were eligible to be enrolled in this study. Participants eligible for PARP inhibitors or had received prior treatments with systemic/hemibody radiotherapy (<6 months ago), immunotherapy (except sipuleucel-T), chemotherapy (except [neo]adjuvant taxane >12 months ago), or biological therapy (including monoclonal antibodies) were ineligible for the study.

This study included male participants ≥ 18 years of age, with mCRPC who were previously treated with ARPI/ARDT as last treatment, had not been exposed to a taxane-containing regimen in the mCRPC or metastatic hormone-sensitive prostate cancer (mHSPC) settings, and who were considered appropriate for delaying taxane-based chemotherapy.

5.2.2.2. Inclusion criteria

Participants included in this study must have met all of the following criteria:

1. Signed informed consent was obtained prior to participation in the study.
2. Participants were adults ≥ 18 years of age.
3. Participants must have had an ECOG performance status of 0 to 1.
4. Participants must have had histological pathological, and/or cytological confirmation of adenocarcinoma of the prostate.
5. **Participants were 68Ga-PSMA-11 (gallium (68Ga) gozetotide (company research code: AAA517); hereinafter referred to as "gallium (68Ga) gozetotide") PET/Computed Tomography (CT) scan positive, and eligible as determined by the sponsor's central reader.**
6. Participants must have had a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L).
7. **Participants had to have progressed only once on prior second-generation ARPI/ARDT (abiraterone, enzalutamide, darolutamide, or apalutamide):**
 - **first generation androgen receptor inhibitor therapy (e.g., bicalutamide) was allowed but not considered as prior ARPI/ARDT therapy,**
 - **Second generation ARPI/ARDT must be the most recent therapy received.**

8. **Participants had to have progressive mCRPC.** Documented progressive mCRPC was based on at least one of the following criteria:

- Serum/plasma PSA progression defined as two consecutive increases in PSA measured at least 1 week apart. The minimal start value was 2.0 ng/mL; 1.0 ng/mL was the minimal starting value if confirmed rise in PSA was the only indication of progression,
- Soft-tissue progression defined [PCWG3-modified RECIST v1.1 (Eisenhauer et al 2009, Scher et al 2016),
- Progression of bone disease: two new lesions; only positivity on the bone scan defined metastatic disease to bone (PCWG3 criteria (Scher et al 2016).

9. **Participants had to have ≥ 1 metastatic lesion** that is present on screening/baseline CT, magnetic resonance imaging (MRI), or bone scan imaging obtained ≤ 28 days prior to beginning study therapy.

10. Participants had to have recovered to $\leq$ Grade 2 from all clinically significant toxicities related to prior therapies (i.e., prior chemotherapy, radiation, etc.) except alopecia.

11. Participants had to have adequate organ function:

- Bone marrow reserve: $\cdot$ ANC $\geq 1.5 \times 10^9/L$, $\cdot$ Platelets $\geq 100 \times 10^9/L$, $\cdot$ Hemoglobin ≥ 9 g/dL.
- Hepatic:
 - Total bilirubin $< 2 \times$ the institutional upper limit of normal (ULN). For participants with known Gilbert' Syndrome $\leq 3 \times$ ULN is permitted,
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN OR $\leq 5.0 \times$ ULN for participants with liver metastases.
- Renal: $\cdot$ eGFR ≥ 50 mL/min/1.73m² using the Modification of Diet in Renal Disease (MDRD) equation.

12. Albumin ≥ 2.5 g/dL.

13. Candidates for change in ARPI/ARDT as assessed by the treating physician,

- Participants must have not been previously progressed nor had intolerable toxicity to both enzalutamide and abiraterone.

5.2.2.3. Exclusion criteria

Participants who met any of the following criteria were not eligible for inclusion in this study:

1. Previous treatment with any of the following within 6 months of randomization: Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation.
2. Previous PSMA-targeted RLT.
3. Prior treatment with cytotoxic chemotherapy for castration resistant or castrate sensitive prostate cancer (e.g., taxanes, platinum, estramustine, vincristine, methotrexate, etc.), immunotherapy or biological therapy [including monoclonal antibodies] [Note: Taxane exposure (maximum 6 cycles) in the adjuvant or neoadjuvant setting was allowed if 12 months have elapsed since completion of this adjuvant or neoadjuvant therapy. Prior treatment with sipuleucel-T was allowed].
4. Any investigational agents within 28 days prior to day of randomization.

5. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar classes.
6. Concurrent cytotoxic chemotherapy, immunotherapy, RLT, Poly (adenosine diphosphate- ribose) polymerase (PARP) inhibitor, biological, or investigational therapy.
7. Transfusion or use of bone marrow stimulating agents for the sole purpose of making a participant eligible for study inclusion.
8. Participants with a history of central nervous system (CNS) metastases that were neurologically unstable, symptomatic, or receiving corticosteroids for the purpose of maintaining neurologic integrity. Participants with CNS metastases were eligible if received therapy (surgery, radiotherapy, gamma knife), asymptomatic and neurologically stable without corticosteroids.

Participants with epidural disease, canal disease and prior cord involvement were eligible if those areas had been treated, were stable, and not neurologically impaired.
9. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
10. History or current diagnosis of the following electrocardiogram (ECG) abnormalities indicating significant risk of safety for study participants:
 - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block),
 - History of familial long QT syndrome or known family history of Torsades de Pointe,
 - Cardiac or cardiac repolarization abnormality, including any of the following: History of MI, angina pectoris, or coronary artery bypass graft within 6 months prior to starting study treatment.
11. Concurrent serious (as determined by the Principal Investigator) medical conditions, including, but not limited to New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation:
 - HIV-infected participants who were at a low risk of AIDS-related outcomes might have participated in this study,
 - Participants with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent might have been included only when completely recovered (in accordance with local guidance).
12. Diagnosed with other malignancies that were expected to alter life expectancy or may interfere with disease assessment. Participants with a prior history of malignancy that were adequately treated and who had been disease free and treatment free for more than 3 years prior to randomization were eligible, as were participants with adequately treated non- melanoma skin cancer, superficial bladder cancer.
13. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 14 weeks after stopping study treatment. A condom was required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period

specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and were described in the Informed Consent Form (ICF).

14. Unmanageable concurrent bladder outflow obstruction or urinary incontinence.

15. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.

16. Any condition that precluded raised arms position.

17. Eligible for treatments other than ARPI/ARDTs based on presence of any mutations or biomarkers that are known as predictors of better response (e.g., AR-V7 or BRCA).

18. Not able to understand and to comply with study instructions and requirements.

5.2.3. Treatments

AAA617 was administered i.v. at a dose of 7.4 GBq (200 mCi) $\pm$ 10% AAA617 once every 6 weeks (1 cycle) for 6 cycles.

The change of ARPI/ARDT treatment included approved AR-axis targeted therapy abiraterone or enzalutamide. ARPI/ARDT treatment was dosed as per approved local labels and guidelines including contraceptive requirements. Abiraterone was to be dosed with prednisone or prednisolone as per the approved local labels.

Supportive care was allowed in both arms and included available care for eligible patients according to best institutional practice for mCRPC treatment, including ADT and palliative radiation at the discretion of the investigator. Antineoplastic radiotherapy during the randomised treatment phase was also summarized by treatment arm.

For participants who did not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions were either recommended or mandated to allow participants to continue the study treatment. Deviations to mandatory dose interruptions and/or reductions were not allowed.

5.2.1. Objectives

5.2.1.1. Outcomes/endpoints

5.2.1.2. Primary estimands

Primary clinical question of interest: what the effect of AAA617 versus ARPI/ARDT with regard to time to radiographic progression or death in the treatment of taxane naive men with progressive PSMA-positive mCRPC is as defined through inclusion/exclusion criteria, regardless of treatment discontinuations for any reasons, change in best supportive care (BSC) or start of new antineoplastic therapy prior to rPFS event.

A treatment policy strategy is applied to mirror the conditions in clinical practice.

The primary estimand is described by the following attributes:

1. Population: all randomised men with progressive PSMA-positive mCRPC, treated with ARPI/ARDT as last treatment that were candidates for ARPI/ARDT change as defined in inclusion criteria and where it was considered appropriate to delay taxane-based chemotherapy.
2. Variable: rPFS
3. Treatment of interest: the investigational treatment is AAA617 with BSC regardless of subsequent anti-neoplastic treatment. The control treatment is ARPI/ARDT with BSC regardless of subsequent anti-neoplastic treatment.
4. Intercurrent events (treatment policy):
 - Discontinuation of study treatment for any reason
 - Change in best supportive care
 - Start of anti-neoplastic therapy prior to radiographic progression
5. Summary measure: rPFS hazard ratio (AAA617 with BSC versus ARPI/ARDT with BSC) along with 95% confidence interval (CI), estimated using a Cox proportional hazard model stratified by the randomisation stratification factors.

5.2.1.3. Secondary estimands

Key secondary clinical question of interest: what is the effect of AAA617 versus ARPI/ARDT with regard to OS in the treatment of taxane naive men with progressive PSMA-positive mCRPC as defined through inclusion/exclusion criteria, regardless of treatment discontinuations for any reasons, change in BSC, switching to AAA617 arm or start of new antineoplastic therapy?

explicit

A treatment policy strategy is applied to mirror the conditions in clinical practice.

The key secondary estimand is described by the following attributes:

1. Population: same as that of primary estimand,
2. Variable: OS,
3. Treatment of interest: the investigational treatment is AAA617 with BSC regardless of subsequent anti-neoplastic treatment and the control treatment was switch in ARPI/ARDT regardless of subsequent anti-neoplastic treatment including crossing over to receive AAA617.
4. Handling of remaining intercurrent events (treatment policy):
 - Discontinuation of study treatment for any reason,
 - Change in best supportive care,
 - Start of new anti-neoplastic therapy,
 - Crossover to AAA617 arm for participants in ARPI/ARDT arm.
5. Summary measure: OS hazard ratio (AAA617 with BSC versus ARPI/ARDT with BSC) along with 95% CI, estimated using a Cox proportional hazard model stratified by the randomisation stratification factors.

5.2.2. Endpoints

5.2.2.1. Primary endpoint

- **rPFS** defined as the time from the date of randomization to the date of first documented radiographic disease progression as assessed by BICR and as outlined in PCWG3 Guidelines (Scher et al 2016) or death due to any cause.

5.2.2.2. Key Secondary

- **OS** defined as time from randomization to death due to any cause.

5.2.2.3. Other Secondary

- **rPFS2 (for crossover patients only)** defined as time from the date of crossover (ARPI/ARDT to AAA617) to the date of radiographic disease progression by BICR or death from any cause (rPFS definition as outlined in PCWG3 guidelines).
- **PFS** defined as time from date of randomization to the first documented **progression by investigator's assessment** (radiographic, clinical, or PSA progression) or death from any cause, whichever occurred first.
- **PFS2** defined as time from date of randomization to the first documented **progression by investigator assessment** (radiographic progression, clinical progression, PSA progression) or death from any cause, whichever occurred first, on next line of therapy.
- **PSA50** defined as proportion of patients who achieved a $\geq 50\%$ decrease from baseline that was confirmed by a second PSA measurement ≥ 4 weeks. PSA50 was evaluated at 12, 24 and 48 weeks, and anytime during the randomised treatment phase.
- **Time to symptomatic skeletal event (TTSSE)** defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurred first. TTSSE was assessed only during study treatment period.
- **Time to soft tissue progression (TTSTP)** defined as time from randomization to radiographic soft tissue progression per PCWG3- modified RECIST v1.1 as BICR.
- **Time to chemotherapy (TTCT)** defined as time from randomization to initiation of the first subsequent chemotherapy or death, whichever occurred first.
- **HRQoL** as assessed by EQ-5D-5L, FACT-P and BPI-SF.

5.2.2.4. Exploratory

- **Overall response rate (ORR)** defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR), as per BICR and according to PCWG3- modified RECIST v1.1.
- **Disease Control Rate (DCR)** defined as the proportion of patients with BOR of CR, PR, stable disease (SD) or non-CR/non-PD by BICR and PCWG3-modified RECIST v1.1 assessment in soft tissue, lymph node and visceral lesions.

- **Duration of response (DOR)** defined as the duration of time between the date of first documented BOR (CR or PR which must be confirmed subsequently) according to PCWG3-modified RECIST v1.1 based on tumour response data per BICR and the date of first documented progression or death due to any cause.
- **Time to response (TTR)** defined as the time from the date of randomization to the date of first documented BOR of CR or PR, which are based on tumour response data as per BICR and according to RECIST v1.1 during the randomised part of the study and prior to further antineoplastic therapy.
- **Time to PSA progression (TTPSAP)** defined as time from randomization to PSA progression. PSA progression date is defined as the date of
 - 1) $\geq 25\%$ increase and ≥ 2 ng/mL above the nadir, confirmed by a second value ≥ 3 weeks later if there is PSA decline from baseline, or
 - 2) $\geq 25\%$ increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks if there is no PSA decline from baseline [Study B12302 IA3-Efficacy assessments]

5.2.2.5. Efficacy assessment

5.2.2.5.1. Radiographic imaging for tumour assessment

Radiologic assessment to monitor radiographic progression followed PCWG3 modified RECIST v1.1 guidelines (Eisenhauer et al 2009, Scher et al 2016, Appendix 16.1.1-Protocol-Section 16.2 and Appendix 16.1.1-Protocol-Section 16.3).

Periodic radiographic imaging included both:

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

CT with contrast/MRI tumour assessments included evaluations of the chest, abdomen, and pelvis. Sites of “soft-tissue” disease were characterized as either target or non-target lesions based on CT/MRI images. A maximum of 5 target lesions per site of metastatic spread (e.g., lung, liver, adrenal glands, lymph nodes, etc.) were chosen for measurement over the course of the study.

Sites of bone disease were recorded based on bone scan, with exception to bone metastasis with soft tissue component which might have qualified for target/non-target when detectable by CT/MRI as described above. Note, that for the purpose of the study, bone lesion(s) were assessed by bone scan only.

Radiographic disease progression was assessed both locally and via blinded centralized review of scheduled and unscheduled scans obtained to evaluate disease for all participants according to PCWG3-modified RECIST v1.1.

Imaging data was centrally collected and checked for quality by an imaging contract research organization designated by Novartis. The results of the central evaluations were used to screen the study participants for eligibility (PET imaging with gallium (68Ga) gozetotide) and for study endpoint analyses (BICR evaluated by conventional imaging). The local investigator’s assessment was used for treatment decision making.

5.2.2.5.2. Clinical progression

Clinical progression was assessed by the investigator by the following criteria:

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

5.2.2.5.3. Assessment of patient reported outcomes

The patient reported outcomes (PRO) measures included Brief Pain Inventory- Short Form (BPI-SF), FACT-P and the EQ-5D-5L and were assessed as per the schedule of assessments.

Pain was assessed using the BPI- SF to assess the severity of pain and the impact of pain on daily functions.

The FACT-P questionnaire was also administered to specifically assess the HRQoL of prostate cancer participants. The FACT-P is made up of 2 parts: the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire with 27 questions, and the prostate cancer subscale (PCS) comprising an additional 12 questions. The PCS is designed specifically to measure prostate cancer-specific quality of life.

The EQ-5D-5L questionnaire was administered to assess a participant's self-reported health status. EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. This instrument generates a preference-based health state utility score (EQ-5D utility index), consisting of 5 dimensions (mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression) and an overall health-state score based on a visual analog scale (EQ-5D VAS).

5.2.3. Sample size

The sample size calculation is based on the primary variable rPFS and key secondary variable OS.

It is expected that treatment with ¹⁷⁷Lu-PSMA-617 and BSC will result in a 44% reduction in the hazard rate for rPFS compared to the control arm i.e., an expected hazard ratio of 0.56, which corresponds to an increase in median rPFS by 4.7 months under the exponential model assumption (from 6 to 10.7 months).

In order to ensure at least 95% power to test any null hypothesis: rPFS hazard ratio = 1, versus the alternative hypothesis: rPFS hazard ratio = 0.56, it is calculated that a total of 156 rPFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, participants randomized to the two treatment arms in a 1:1 ratio.

Assuming that enrolment will continue for 10.5 months at a non-uniform rate for a total of 450 patients and losses to follow-up for rPFS of approximately 10% and 20% in the [¹⁷⁷Lu]Lu- PSMA-617 and BSC and control arm, respectively, the targeted 156 rPFS events are expected to occur at about 3

months after the randomization date of the last participant OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable rPFS is statistically significant.

Overall, a total study sample size of approximately 450 participants was considered sufficient to be randomly assigned to each treatment arm in a 1:1 ratio (225 participants in [177Lu]Lu-PSMA-617 with BSC arm and 225 participants in ARDT with BSC arm).

5.2.4. Randomisation

Randomisation by stratification factor

According to the study report, as eligible participants were randomised via Interactive Response Technology (IRT) to one of the arms in a 1:1 ratio: AAA617 or change in comparator approved ARPI/ARDT (abiraterone or enzalutamide). The investigator or his/her delegate contacted the IRT after confirming that the participant fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomization number to the participant, which was used to link the participant to a treatment arm. The change of ARPI/ARDT treatment for each participant was selected by the treating physician prior to randomization. If the participant was randomised to receive AAA617, the choice of change of ARPI/ARDT treatment was discarded.

Randomisation was stratified based on prior ARPI/ARDT use and symptomatology. As expected, the proportion of participant within each of the stratification factors was balanced between AAA617 and ARPI/ARDT arms. Summary of randomisation by stratification factor is presented in Table 10-1.

Table 10-1 Randomisation by stratification factor (FAS)

Randomisation by stratification factor	[177Lu]Lu-PSMA-617 N=234 n (%)	ARDT N=234 n (%)	All Participants N=468 n (%)
Prior ARDT use			
Castrate resistant prostate cancer (CRPC) setting	190 (81.2)	190 (81.2)	380 (81.2)
Hormone sensitive prostate cancer (HSPC) setting	44 (18.8)	44 (18.8)	88 (18.8)
Symptomatology			
Asymptomatic or mildly symptomatic	165 (70.5)	166 (70.9)	331 (70.7)
Symptomatic	69 (29.5)	68 (29.1)	137 (29.3)
Prior ARDT use and Symptomatology			
CRPC + Asymptomatic or mildly symptomatic	136 (58.1)	137 (58.5)	273 (58.3)
CRPC + Symptomatic	54 (23.1)	53 (22.6)	107 (22.9)
HSPC + Asymptomatic or mildly symptomatic	29 (12.4)	29 (12.4)	58 (12.4)
HSPC + Symptomatic	15 (6.4)	15 (6.4)	30 (6.4)

Strata as entered in the IRT at the time of randomisation.

Asymptomatic or mildly symptomatic is defined as having a score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire.

Symptomatic is defined as having a score > 3 on item 3 of the BPI-SF questionnaire. Data cut-off date: 27-Feb-2024

Source: Table 14.1-1.3

Per the IRT system, 380 participants (81.2%) received prior ARPI/ARDT in the CRPC setting, 88 participants (18.8%) in the HSPC setting. A total of 331 participants (70.7%) were asymptomatic or mildly symptomatic, and 137 participants (29.3%) were symptomatic at baseline.

Per the CRF, 356 participants (76.1%) received prior ARPI/ARDT in the CRPC setting, 111 participants (23.7%) in the HSPC setting. A total of 254 participants (54.3%) were asymptomatic or mildly symptomatic, and 167 participants were symptomatic (35.7%) at baseline.

For overall participants, the concordance rate for randomisation by stratification factor was 85% for prior ARPI/ARDT and 77% for symptomatology

In both arms, >80% of the participants had prior ARPI/ARDT use in CRPC setting and >70% of the participants were asymptomatic or mildly symptomatic in Ga-PSMA-11 FAS, FAS, safety set, and Lu-PSMA-617 safety set.

5.2.5. Blinding (masking)

Treatment assignment was **open to participants, investigator staff, persons performing the assessments, and the Novartis study team**. To minimize the potential impact on the integrity of the study, until the primary analysis was conducted, no aggregate statistical analyses (efficacy or safety across the study) were performed by treatment arm. **Central imaging reviewers remained blinded to the identity of the randomised treatment**

5.2.6. Statistical methods

The Full Analysis Set (FAS) comprised all participants to whom study treatment was assigned by randomisation. According to the intent to treat (ITT) principle, participants were analyzed according to the treatment and strata they were assigned to during the randomisation procedure.

The FAS was the primary population for all efficacy analyses, unless otherwise specified. The Safety Set included all participants who received at least one dose of study treatment (i.e., at least one dose of (AAA617 or ARPI/ARDTs) during the randomised part of the protocol. Participants were analyzed according to the study treatment received, where treatment received was defined as the randomised treatment if the participant took at least one dose of that treatment.

The Crossover Analysis Set (CAS) consisted of participants randomised to the ARPI/ARDT arm who crossed over after BICR-confirmed radiographic progression to receive at least one dose of AAA617. This analysis set was used for all analyses (rPFS2) pertaining to rPFS data collected after participants crossed over to receive AAA617.

The RECIST Analysis Set (RAS) consisted of the subset of participants in the FAS with evaluable soft tissue disease by PCWG3-modified RECIST v1.1 at baseline, defined as having at least one lesion (target or non-target) identified at baseline in soft tissue. Participants were included in the treatment arm to which they were randomised. This analysis set was used for the analysis of RECIST-based endpoints (e.g., TTSTP, ORR, DOR, etc.).

The Ga-PSMA-11 Full Analysis set (Ga-FAS) included all participants who received the administration of gallium (68Ga) gozetotide. This analysis set was the basis of safety and imaging summaries for the gallium (68Ga) gozetotide specific analyses. This included all screened participants who received gallium (68Ga) gozetotide and were randomised, and those who received gallium (68Ga) gozetotide but not randomised.

The Lu-PSMA-617 Safety Set included all participants who received at least one dose of AAA617, during the randomised part of the protocol or after crossover. This analysis set was used for safety analyses.

5.2.6.1. Primary rPFS Analysis

Assuming proportional hazards for rPFS, the following statistical hypothesis was tested to address the primary efficacy objective:

$H_{01}: \theta_1 \geq 1$ vs. $H_{A1}: \theta_1 < 1$

where θ_1 is the rPFS HR (AAA617 arm versus ARPI/ARDT arm).

A stratified log-rank test at an overall one-sided 2.5% level of significance was used to test the primary hypothesis. The stratification was based on the randomisation stratification factors, i.e., setting of prior ARPI/ARDT: CRPC vs HSPC; symptomatology based on item 3 of the BPI-SF questionnaire: asymptomatic and mildly symptomatic (score of 0-3) vs symptomatic (score of > 3).

rPFS analyses were based on the FAS population according to the randomised treatment arm and strata assigned at randomisation (as obtained via IRT). The rPFS distribution was estimated using the K-M method, and K-M curves, medians and 95% CIs of the medians were presented for each treatment arm. The HR for rPFS was calculated, along with its 95% CIs, from a stratified Cox model using the same stratification factors as for the log-rank test.

The sensitivity, supplementary and subgroup analyses for rPFS were conducted based on various factors.

The primary rPFS analysis was carried out after 166 rPFS events (60 events in AAA617 arm and 106 events in ARPI/ARDT arm) were observed. An additional rPFS analysis was conducted at the time of the third OS interim analysis.

5.2.6.2. Key secondary endpoint: OS Analysis

Assuming a proportional hazards model for OS, the following statistical hypothesis was tested only if rPFS was statistically significant:

$H_{02}: \theta_2 \geq 1$ vs. $H_{A2}: \theta_2 < 1$

where θ_2 is the OS HR (AAA617 arm versus ARPI/ARDT arm).

A stratified log-rank test at an overall one-sided 2.5% level of significance analysis was performed to test the hypothesis.

A 4-look group sequential design was considered for OS.

The type I error probability was controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function for OS which is independent of the one used for rPFS. This guarantees the protection of the overall type I error ($\alpha = 2.5\%$) across all hypotheses and the repeated testing of the OS hypotheses at the interim and the final analyses.

The key secondary endpoint, OS was analyzed following the ITT principal based on the FAS population following the intent-to-treat principle according to the treatment arm and strata assigned at randomisation. The OS distribution was estimated using the K-M method, and KM curves, medians and 95% CIs of the medians were presented for each treatment arm. The HR for OS was calculated, along

with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test.

The rank preserving structural failure time (RPSFT) model was used as the prespecified method to adjust OS for confounding due to crossover, however, other methods including Inverse Probability of Censoring Weighting (IPCW) proposed by were also used based on an examination of the appropriateness of the data to the assumptions required by the methods.

Other secondary endpoint analysis

Other secondary endpoints including time to SSE, ORR, DCR, DOR, Proportion of participants who had achieved a $\geq 50\%$ decrease from baseline that is confirmed by a second PSA measurement ≥ 4 weeks (PSA50 response), time to PSA progression, and HRQoL (FACT-P, BPI-SF, EQ-5D-5L) were also be analyzed.

Safety analysis

Safety analysis set was used to analyze the safety data. AEs were summarized by number and percentage of participants having at least one AE, having at least one AE in each SOC and for each PT using MedDRA coding (Version 26.1). Summaries of these safety topic of interests were provided by treatment arm (when applicable), (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.). Laboratory data from all sources (central and local laboratories) were combined.

The summaries included all assessments available for the lab parameter collected during the on-treatment period. ECG and vital signs data were summarized.

5.2.7. Results

Participant flow

Not submitted, but see 'Supplementary Figure S1. CONSORT diagram' of [Fizazi et al. Ann Oncol. 2025](#).

Recruitment

Study centers: 72 centers across 14 countries participated in the study: Austria (3 centers), Belgium (4 centers), Canada (3 centers), Czech Republic (1 center), France (6 centers), Germany (2 centers), Netherlands (3 centers), Poland (1 center), Slovakia (1 center), Spain (15 centers), Sweden (3 centers), Switzerland (3 centers), United Kingdom (7 centers), the United States (20 centers).

Study period:

Study initiation date: 15-Jun-2021 (first participant first visit)

Data cut-off dates: 02-Oct-2022 (primary analysis); 27-Feb-2024 (Interim OS analysis); 01-Jan-2025 (final OS analysis)

Conduct of the study

Protocol amendments and other changes to study conduct: (according to the final protocol amendment version 03.)

Original protocol (Version 00) was dated 03-Nov-2020.

Protocol amendment 01 was finalized on 13-Jan-2022 to include key updates in imaging assessments, schedule of assessment table, crossover procedure, screening period for assessments prior to randomisation, and potential drug interaction with ARPI/ARDT.

Protocol amendment 02 was finalized on 04-Aug-2022 to include key updates in discontinuation process, exclusion criteria, safety follow-up, AE reporting, dosimetry schedule and physical examination schedule.

Protocol amendment 03 was finalized on 21-Feb-2023 to include additional interim analysis for OS after the occurrence of approximately 125 events and section on-treatment overdose.

Production halt at the RLT production sites

On 04-May-2022, there was a production halt at the RLT production sites in Ivrea, Italy and Millburn, New Jersey out of an abundance of caution whilst internal investigations were conducted.

No study drug was available globally. The drug shortage led to the declaration of a USM as this event could potentially affect the safety of study participants. The USM resulted in the following actions:

- Voluntary temporary halt of enrolment, including screening (to prevent participants to be unnecessarily exposed to screening assessments and other protocol-mandated procedures, including gallium (68Ga) gozetotide injection and PSMA PET imaging).
- Provide benefit-risk-led recommendations to investigators on how to manage participants under screening or treatment or participants eligible for crossover to investigational treatment.
- Production resumed in Millburn on 29-May-2022 and in Ivrea on 05-Jun-2022. Notice of the lift of the enrolment halt was distributed to site clinical research associates (CRAs) on 25-May-2022.

Protocol violations are sufficiently described and assessment of the details raised not specific concerns as source of bias.

5.2.7.1. Baseline data

Table 3-2 Patient disposition (Full Analysis Set): DCO 27-Feb-2024

Disposition Reason	[¹⁷⁷Lu]Lu-PSMA-617 N=234 n (%)	ARDT N=234 n (%)	All Patients N=468 n (%)
Patients randomized	234 (100)	234 (100)	468 (100)
Treated	227 (97.0)	232 (99.1)	459 (98.1)
Not treated Reason for not being treated	7 (3.0)	2 (0.9)	9 (1.9)
Patient decision	3 (1.3)	1 (0.4)	4 (0.9)
Adverse event	3 (1.3)	0	3 (0.6)
Physician decision	1 (0.4)	0	1 (0.2)
Protocol deviation	0	1 (0.4)	1 (0.2)
Treatment ongoing *	0	20 (8.5)	20 (4.3)
Completed treatment	131 (56.0)	0	131 (28.0)
Discontinued from treatment	96 (41.0)	212 (90.6)	308 (65.8)

Disposition Reason	[¹⁷⁷Lu]Lu-PSMA-617 N=234 n (%)	ARDT N=234 n (%)	All Patients N=468 n (%)
Reason for discontinuation			
Progressive disease	54 (23.1)	163 (69.7)	217 (46.4)
Physician decision	23 (9.8)	31 (13.2)	54 (11.5)
Adverse event	13 (5.6)	11 (4.7)	24 (5.1)
Patient decision	5 (2.1)	6 (2.6)	11 (2.4)
Death	0	1 (0.4)	1 (0.2)
Lost to follow-up	1 (0.4)	0	1 (0.2)
Entered crossover treatment period		134 (57.3)	134 (28.6)
Treatment ongoing *		7 (3.0)	7 (1.5)
Completed treatment		55 (23.5)	55 (11.8)
Discontinued from treatment		72 (30.8)	72 (15.4)
Reason for discontinuation			
Progressive disease		42 (17.9)	42 (9.0)
Physician decision		17 (7.3)	17 (3.6)
Adverse event		5 (2.1)	5 (1.1)
Patient decision		5 (2.1)	5 (1.1)
Death		3 (1.3)	3 (0.6)

* Ongoing at the time of the data cut-off date of 27-Feb-2024.

One patient who was randomized and treated with [¹⁷⁷Lu]Lu-PSMA-617 is excluded from the FAS due to PD 'INCL01A' (informed consent not obtained per due process) [Study B12302 IA3-Listing 16.2.1-1.1].

Source: [Study B12302 IA3-Table 14.1-1.2]

At the time of the primary rPFS analysis, using a DCO of 02-Oct-2022, the study was ongoing (Table 3-3). The median duration of study (from randomization to data cut-off) was 7.3 months for each arm. A high proportion of patients had a relatively short follow-up; a total of 125 patients (53.6%) in the AAA617 arm vs. 97 patients (41.5%) in the ARPI/ARDT arm were censored as "ongoing without event" prior to the median duration of study in each treatment arm

Table 3-3 Summary of duration between randomization and cut-off date (Full Analysis Set): DCO 02-Oct-2022

	[¹⁷⁷Lu]Lu-PSMA-617 N=233	ARDT N=234	All Patients N=467
Time from last patient randomized to cut-off date (months)	0.8	0.7	0.7
Duration between randomization and cut-off date (months)			
N	233	234	467
Mean (SD)	7.23 (3.890)	7.23 (3.915)	7.23 (3.898)
Median	7.26	7.28	7.26
Q1-Q3	3.38 - 10.74	3.38 - 10.51	3.38 - 10.55
Min-max	0.8 - 15.1	0.7 - 15.1	0.7 - 15.1

Duration between randomization and data cut-off date = (Cut-off date - Date of randomization (enrollment) + 1)/30.4375 (months).

Source: [Study B12302 IA3-Table 14.2-2.4a]

At the time of final OS analysis, based on a DCO of 01-Jan-2025, the study was ongoing. The median duration of study (from randomization to data cut-off) was 34.3 months (range: 26.9 -42.1) in AAA617 arm vs 34.2 months (range: 27.7 - 42.2) in the ARPI/ARDT arm [Study B12302 IA4-Table 14.2-2.4b].

Table 3-4 Summary of duration between randomization and cut-off date (Full Analysis Set): DCO 27-Feb-2024

	[177Lu]Lu-PSMA-617 N=234	ARDT N=234	All Patients N=468
Time from last patient randomized to cut-off date (months)	16.7	17.5	16.7
Duration between randomization and cut-off date (months)			
N	234	234	468
Mean (SD)	24.05 (3.911)	24.08 (3.915)	24.07 (3.909)
Median	24.11	24.13	24.11
Q1-Q3	20.24 - 27.60	20.24 - 27.37	20.24 - 27.40
Min-Max	16.7 - 32.0	17.5 - 32.0	16.7 - 32.0

Duration between randomization and data cut-off date = (Cut-off date - Date of randomization (enrollment) +1)/30.4375 (months). Source: [Study B12302 IA3-Table 14.2-2.4b]

At the time of final OS analysis, based on a DCO of 01-Jan-2025, the study was ongoing. The median duration of study (from randomization to data cut-off) was 34.3 months (range: 26.9 - 42.1) in AAA617 arm vs 34.2 months (range: 27.7 - 42.2) in the ARPI/ARDT arm [Study B12302 IA4-Table 14.2-2.4b].

5.2.7.2. Demographics at baseline and other baseline characteristics

As anticipated for the mCRPC population in this study, a high proportion of patients (79.9%) were elderly (≥ 65 years), and the median age was 72 years (range: 43-94). All study sites were in Europe or North America (the USA and Canada), and most patients recruited were White (91.0%); Black or African American and Asian patients accounted for only 2.6% and 0.6% of the FAS, respectively [Study B12302 IA3-Table 14.1-4.1].

Baseline characteristics were balanced between the two arms except for a slightly higher proportion of patients with ECOG performance status of 0 (vs. 1) in the AAA617 arm compared to the ARPI/ARDT arm (ECOG 0: 62.4% vs. 49.6%; ECOG 1: 36.8% vs. 48.7%) [Study B12302 IA3- Section 10.4.2]. At the time of diagnosis, 44.9% of patients in each arm had stage IV cancer.

All patients had an advanced disease with Stage IV cancer at the time of study entry, and most patients in the FAS had an initial Gleason score of ≥ 6 . Bone was the most common metastatic site (87.2% of patients). The median (min, max) time since initial diagnosis of prostate cancer was 5.45 (0.6, 28.6) years in the AAA617 arm and 6.80 years (0.7, 27.8) in the ARPI/ARDT arm [Study B12302 IA3-Table 14.1-4.1 and Table 14.1-5.1].

Randomization was stratified by setting of prior ARPI/ARDT use and symptomatology; as expected, the proportion of patients within each of the stratification factors was balanced between the AAA617 and ARPI/ARDT arms. The concordance rate for randomization by stratification factor was 85% for prior ARPI/ARDT and 77% for symptomatology (Table 3-5). In both treatment arms, > 80% of patients had prior ARPI/ARDT use in CRPC setting and > 70% of the patients were asymptomatic or mildly

symptomatic in the FAS, gallium (68Ga) gozetotide FAS, Safety Set, and Lu-PSMA- 617 Safety Set [Study B12302 IA3-Table 14.1-2.1].

Of note, there were two stratification factors for analyses applied to the study data: setting of prior ARPI/ARDT use (CRPC vs HSPC) vs symptomatology defined by BPI-SF at screening (asymptomatic/mildly symptomatic vs symptomatic). Overall, the concordance rate for randomization by stratification factor between IRT and CRF was 85% for prior ARPI/ARDT and 77% for symptomatology (Table 3-5). Stratified analyses were performed using the data from IRT.

Table 3-5 Stratification factors per IRT vs. stratification based on values collected on CRF (Full Analysis Set): DCO 27-Feb-2024

As per IRT						
	[¹⁷⁷ Lu]Lu-PSMA-617 N=234		ARDT N=234		All Patients N=468	
Stratification factor as per CRF data	A	B	A	B	A	B
	n (%)	n(%)	n (%)	n (%)	n (%)	n (%)
Prior ARDT use						
CRPC setting (A)	165 (70.5)	12 (5.1)	168 (71.8)	11 (4.7)	333 (71.2)	23 (4.9)
HSPC setting (B)	25 (10.7)	32 (13.7)	21 (9.0)	33 (14.1)	46 (9.8)	65 (13.9)
Missing	0	0	1 (0.4)	0	1 (0.2)	0
Symptomatology						
Asymptomatic or mildly symptomatic (A)	116 (49.6)	3 (1.3)	129 (55.1)	6 (2.6)	245 (52.4)	9 (1.9)
Symptomatic (B)	30 (12.8)	59 (25.2)	22 (9.4)	56 (23.9)	52 (11.1)	115 (24.6)
Missing	19 (8.1)	7 (3.0)	15 (6.4)	6 (2.6)	34 (7.3)	13 (2.8)

Asymptomatic or mildly symptomatic is defined as having a score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire.

Symptomatic is defined as having a score > 3 on item 3 of the BPI-SF questionnaire. Source: [Study B12302 IA3-Table 14.1-1.4]

Overall, the concordance rate for randomization by stratification factor between IRT and CRF was 85% for prior ARPI/ARDT and lower with 77% for symptomatology.

Exposure duration

At the time of IA3 (DCO 27-Feb-2024), the median (min-max) duration of exposure to study treatment was 8.4 months (0.36-11.63) in the AAA617 arm and 6.5 months (0.03-29.24) in the ARPI/ARDT arm (prior to crossover) (Table 3-6). The median duration of exposure was 6.4 months (0.69 – 29.24) for patients who received abiraterone, and 6.6 months (0.03 – 29.04) for patients who received enzalutamide. The median number of injections was 6 (1 - 6) in the AAA617 arm.

At the time of final OS analysis (DCO 01-Jan-2025), the median (min-max) duration of exposure to study treatment remained similar to the IA3 analysis. The median duration of exposure was 7.2 months (0.49-11.04) for the 141 crossover patients

5.2.7.3. Numbers analysed

Analysis set for IA3 is presented in Table 3-1.

Table 3-1 Analysis sets (all screened patients): DCO 27-Feb-2024

		[¹⁷⁷Lu]Lu-PSMA-617 Full analysis set N=234	ARDT Full analysis set N=234	All Patients Full analysis set N=468
	Screen Failures N=116			
	n (%)	n (%)	n (%)	n (%)
Analysis set				
Gallium (⁶⁸ Ga) gozetotide FAS	79 (68.1)	234 (100)	234 (100)	468 (100)
FAS		234 (100)	234 (100)	468 (100)
Safety Set		227 (97.0)	232 (99.1)	459 (98.1)
Crossover Analysis Set		0	134 (57.3)	134 (28.6)
RECIST Analysis Set		104 (44.4)	102 (43.6)	206 (44.0)
Lu-PSMA-617 Safety Set		227 (97.0)	134 (57.3)	361 (77.1)

Screen failures are those patients that were screened, but not randomized.

[1] N in 'Screen Failures' column is the number of screen failures.

[2] N in the rest of the columns is the number of FAS patients in each treatment group.

[3] Denominator for 'FAS', 'Safety Set', 'Crossover analysis set', 'RECIST analysis set', 'gallium (⁶⁸Ga) gozetotide FAS', 'Lu-PSMA-617 safety set' is 'N' of that column.

One patient randomized and treated with [¹⁷⁷Lu]Lu-PSMA-617 is excluded from all respective analysis sets due to PD 'INCL01A'.

Gallium (⁶⁸Ga) gozetotide FAS included all patients who received gallium (⁶⁸Ga) gozetotide administration. FAS included all patients randomized to study treatment.

Safety Set included all patients who received ≥ 1 dose of the study treatment.

Crossover analysis set included all patients randomized to ARPI/ARDT arm who receive ≥ 1 dose of [¹⁷⁷Lu]Lu-PSMA-

617 as crossover therapy after BICR-confirmed radiographic progression.

RECIST analysis set included those patients with evaluable soft tissue disease at baseline per PCWG3-modified RECIST v1.1.

Lu-PSMA-617 safety set included all patient who received ≥ 1 dose of [¹⁷⁷Lu]Lu-PSMA-617 including as crossover therapy.

Source: [Study B12302 IA3-Table 14.1-2.1]

5.2.8. Outcomes and estimation

Primary efficacy endpoint

5.2.8.1. Primary Endpoint: Radiographic progression-free survival: DCO 02-Oct-2022

The study met its primary objective of prolonging rPFS. At the primary analysis (using DCO of 02-Oct-2022), a statistically significant and clinically meaningful benefit in rPFS was observed in favour of the AAA617 arm (HR = 0.41; 95% CI: 0.29, 0.56; one-sided p-value: < 0.0001) with an estimated 59% reduction in the risk of radiographic progression or death (**Table 3-7, Figure 3-1**).

The estimated median rPFS was 9.30 months (95% CI: 6.77, NE) in the AAA617 arm vs. 5.55 months (95% CI: 4.04, 5.95) in the ARPI/ARDT arm ([Table 3-7](#)).

There were 60 events (25.8%; 53 radiographic progression events and 7 deaths) in the AAA617 arm, and 106 events (45.3%; 99 radiographic progression events and 7 deaths) in the ARPI/ARDT arm

(Table 3-7). A higher proportion of patients were censored in the AAA617 arm compared to the ARPI/ARDT arm (74.2% vs. 54.7%); the primary reason for censoring was “ongoing without event” (AAA617 arm: 66.1% vs. ARPI/ARDT arm: 48.7%).

The K-M curves for rPFS diverged after approximately 8 weeks, corresponding to the time of first tumour assessment, with the estimated rPFS event free probability remaining higher in the AAA617 arm than the ARPI/ARDT arm, indicating an early and sustained advantage for AAA617 treatment (Table 3-7, Figure 3-1). Of note, the estimated rPFS event free probability at 6 months was 69.0% in the AAA617 arm compared with 40.6% in the ARPI/ARDT arm indicating that a larger proportion of patients derived a longer benefit in the AAA617 arm relative to the ARPI/ARDT arm.

Table 3-7 Analysis of radiographic progression-free survival based on blinded independent central review using the Kaplan-Meier method (Full Analysis Set): DCO 02-Oct-2022

	[177Lu]Lu-PSMA-617 N=233	ARDT N=234
Number of events - n(%)	60 (25.8)	106 (45.3)
Radiographic progression	53 (22.7)	99 (42.3)
Death [1]	7 (3.0)	7 (3.0)
Number censored - n(%)	173 (74.2)	128 (54.7)
Ongoing without event [2]	154 (66.1)	114 (48.7)
Adequate assessment no longer available [3]	10 (4.3)	7 (3.0)
Withdrew consent	3 (1.3)	3 (1.3)
Event documented after two or more missing tumour assessments	6 (2.6)	4 (1.7)
Lost to follow-up [4]	0	0
Hazard ratio (95% CI) [177Lu]Lu-PSMA-617 vs. ARDT [5]	0.41 [0.29, 0.56]	
P-value [177Lu]Lu-PSMA-617 vs. ARDT [6]	0.00000001	
Percentiles (95% CI)		
25th	4.40 [3.42, 6.05]	2.30 [2.10, 2.83]
50th (Median)	9.30 [6.77, NE]	5.55 [4.04, 5.95]
75th	12.62 [11.96, NE]	8.64 [6.24, NE]
Kaplan-Meier estimates (%) (95% CI)		
3 months	83.3 [76.7, 88.2]	68.3 [60.8, 74.6]
6 months	69.0 [60.7, 75.9]	40.6 [32.1, 48.8]
9 months	53.1 [41.9, 63.1]	21.6 [13.2, 31.3]
12 months	33.3 [9.6, 59.8]	18.5 [10.0, 29.0]

NE: not estimable.

[1] Death without radiographic progression.

[2] Patients without event and had adequate follow-up as of DCO.

[3] Patients censored without adequate evaluations for a specified period prior to DCO or without adequate baseline assessment.

[4] Recorded on the End of treatment or End of post-treatment follow-up disposition CRF.

[5] Hazard ratio obtained from stratified Cox PH model.

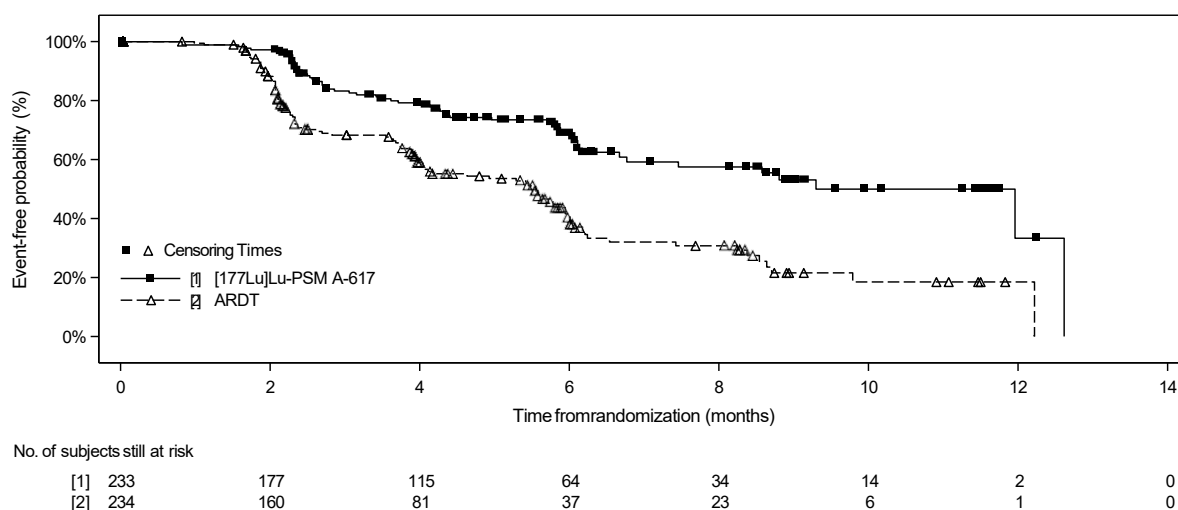
[6] One-sided p-value at 2.5% level of significance obtained from stratified log-rank test.

Stratification factors from IRT data :prior ARDT use in CRPC vs. HSPC; asymptomatic and mildly symptomatic per stratification entered at randomisation in IRT (score of 0-3 on item 3 of the Brief Pain

Inventory Short Form (BPI-SF) questionnaire) vs. symptomatic (score >3 on item 3 of the BPI-SF questionnaire).

Source: [Study B12302 IA3-Table 14.2-1.1a]

Figure 3-1 Kaplan-Meier plot of radiographic progression-free survival based on blinded independent central review (Full Analysis Set): DCO 02-Oct- 2022



Source: [Study B12302 IA3-Figure 14.2-1.1a]

Sensitivity analyses of primary endpoint: DCO 02-Oct-2022

Sensitivity analyses (as defined in [Study B12302 IA3-Section 9.7.6.5]) of rPFS showed results consistent with the primary analysis favouring the AAA617 arm, with an HR ranging from 0.38 to 0.46, and thus demonstrated the robustness of the primary analysis HR estimate (Table 3-8) and [Study B12302 IA3-Figure 14.2-1.3a] .

Table 3-8 Sensitivity analysis of Cox regression model for rPFS comparison of treatment with control (Full analysis set): DCO 02-Oct-2022

	Events/N (%)	Median Time (95% CI) (months) ^[1]	Hazard Ratio (95% CI) ^[2]
Actual stratification			
ARDT	93/212 (43.9)	5.55 (4.04, 5.95)	
[177Lu]Lu-PSMA-617	52/207 (25.1)	12.62 (6.67, NE)	0.39 (0.27, 0.55)
Treatment start			
ARDT	106/232 (45.7)	5.42 (3.75, 5.59)	
[177Lu]Lu-PSMA-617	59/226 (26.1)	11.43 (7.00, NE)	0.46 (0.33, 0.64)
Previous theoretical date			
ARDT	107/234 (45.7)	5.55 (3.75, 5.55)	
[177Lu]Lu-PSMA-617	59/233 (25.3)	11.96 (9.30, NE)	0.45 (0.33, 0.63)
Investigator assessment			
ARDT	82/234 (35.0)	6.24 (5.82, 8.31)	
[177Lu]Lu-PSMA-617	50/233 (21.5)	12.62 (8.80, NE)	0.46 (0.32, 0.65)
Actual event			

	Events/N (%)	Median Time (95% CI) (months) ^[1]	Hazard Ratio (95% CI) ^[2]
ARDT	110/234 (47.0)	5.55 (4.07, 5.98)	
[177Lu]Lu-PSMA-617	66/233 (28.3)	9.30 (6.77, 12.16)	0.42 (0.31, 0.58)
Backdating			
ARDT	110/234 (47.0)	5.45 (3.98, 5.78)	
[177Lu]Lu-PSMA-617	66/233 (28.3)	11.96 (6.18, NE)	0.42 (0.31, 0.58)
New anticancer therapy			
ARDT	104/234 (44.4)	5.55 (4.04, 5.95)	
[177Lu]Lu-PSMA-617	56/233 (24.0)	11.96 (6.77, NE)	0.38 (0.27, 0.53)
Censoring COVID-19 related deaths 'a'			
ARDT	106/234 (45.3)	5.55 (4.04, 5.95)	
[177Lu]Lu-PSMA-617	59/233 (25.3)	11.96 (6.77, NE)	0.40 (0.29, 0.56)
Censoring COVID-19 related deaths 'b'			
ARDT	106/234 (45.3)	5.55 (4.04, 5.95)	
[177Lu]Lu-PSMA-617	59/233 (25.3)	11.96 (6.77, NE)	0.40 (0.29, 0.56)
Censoring for withdrawal of consent at the time of withdrawal			
ARDT	106/234 (45.3)	5.55 (4.04, 5.98)	
[177Lu]Lu-PSMA-617	60/233 (25.8)	11.96 (6.77, NE)	0.41 (0.30, 0.57)
Treating withdrawal of consent as an event at the time of withdrawal			
ARDT	109/234 (46.6)	5.52 (4.04, 5.95)	
[177Lu]Lu-PSMA-617	63/233 (27.0)	9.30 (6.77, NE)	0.42 (0.31, 0.58)
Censoring for delayed treatment start at the time of randomisation			
ARDT	103/234	(44.0)	5.55
[177Lu]Lu-PSMA-617	46/233 (19.7)	11.96 (7.46, NE)	0.38 (0.27, 0.55)

[1] Median rPFS and its 95% CI are generated by KM estimation.

[2] Hazard ratio obtained from stratified Cox PH model.

a : COVID-19 related deaths are censored at the last adequate tumour assessment prior to death.

b : COVID-19 related deaths are censored at the date of death.

Actual stratification is based on non-missing CRF data (both stratification factors are non-missing).

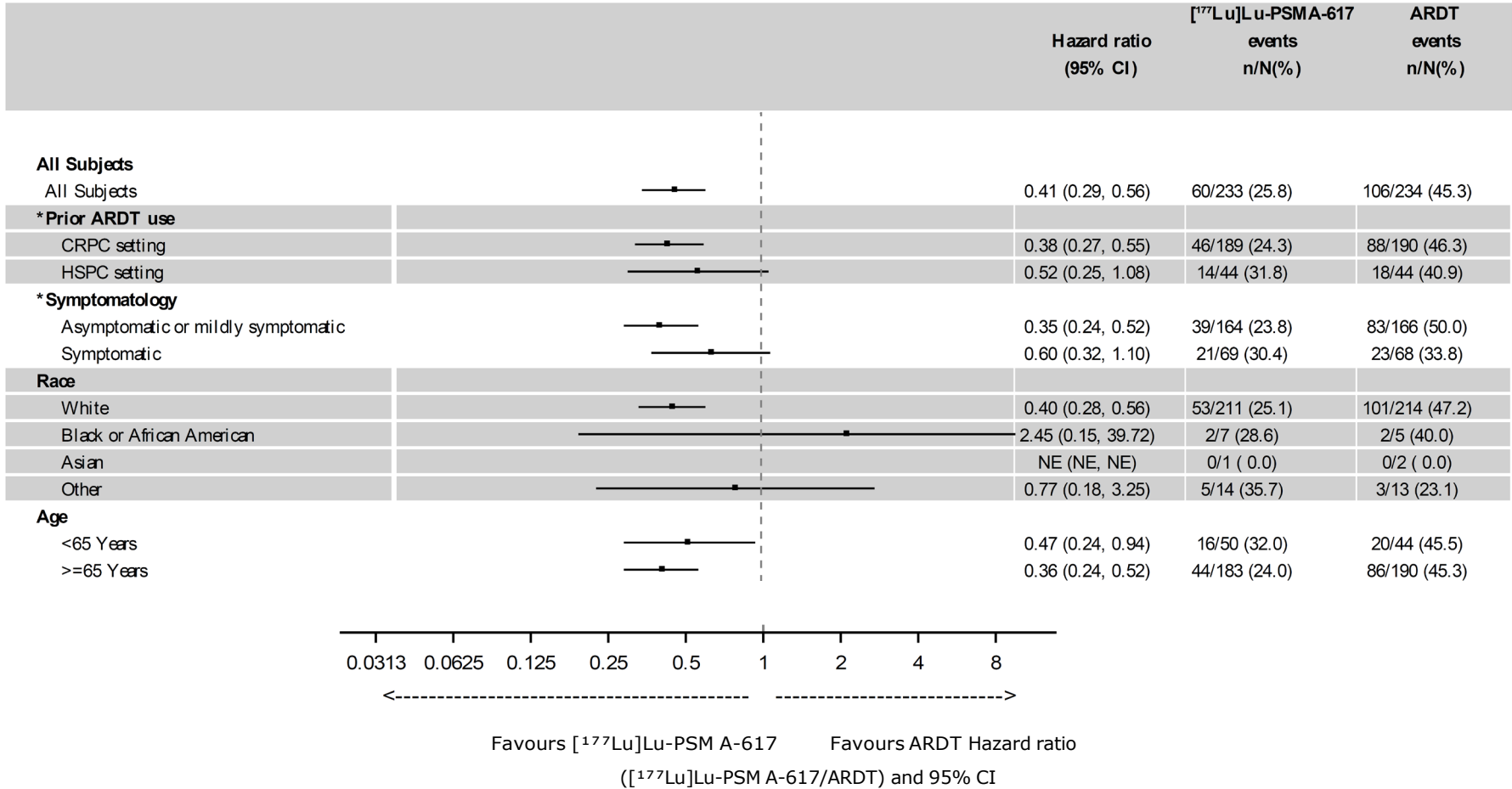
Stratification factors from IRT data: prior ARDT use in CRPC vs. HSPC; asymptomatic or mildly symptomatic per stratification entered at randomisation in IRT (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs. symptomatic (score >3 on item 3 of the BPI-SF questionnaire).

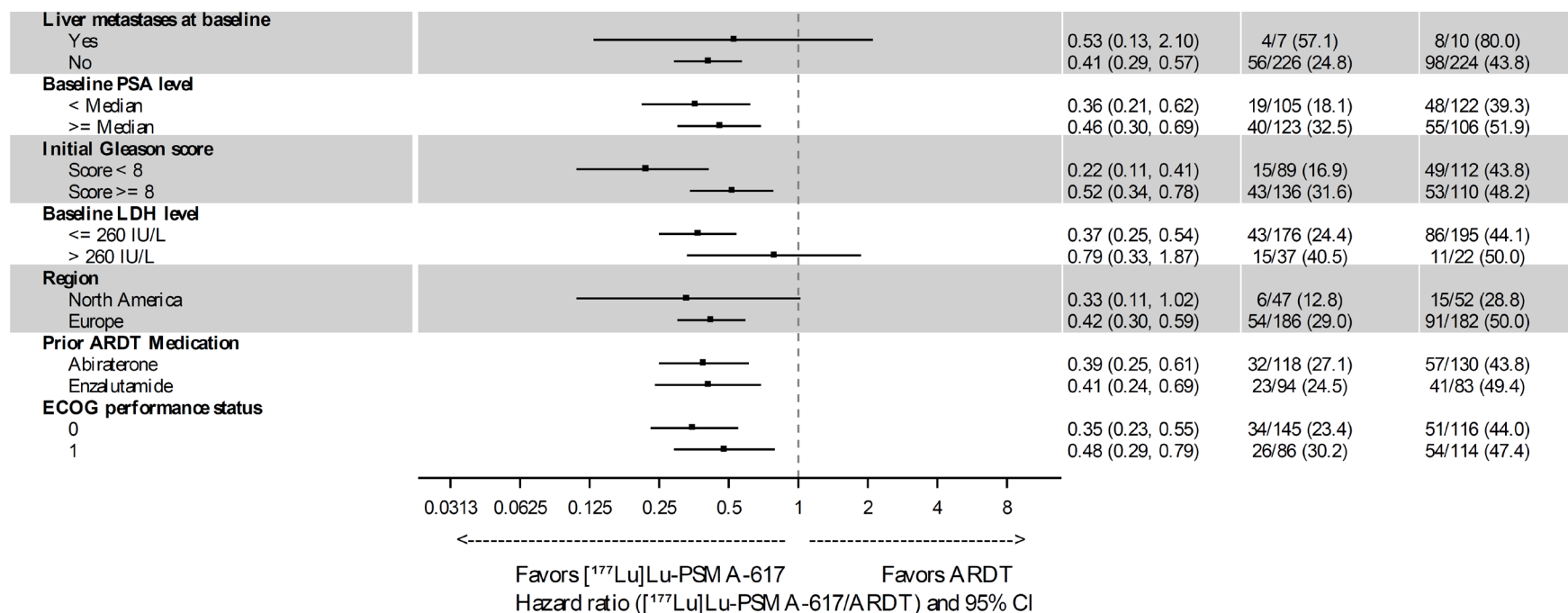
Source: [Study B12302 IA3-Table 14.2-1.3a]

Subgroup analyses of primary endpoint: DCO 02-Oct-2022

Subgroup analyses of rPFS based on pre-specified baseline characteristics showed consistent results with the primary analysis favouring the AAA617 arm vs. the ARPI/ARDT arm (HRs ranging from 0.22 to 0.79) across all subgroups and demonstrating the homogeneity of treatment effect, except for Black or African/American patients (HR = 2.45; 95% CI: 0.15, 39.72), for which the number rPFS events and number of patients were limited, preventing any meaningful conclusions from being drawn (see [Figure 3-2](#) and [Study B12302 IA3-Table 14.2-1.4a]).

Figure 3-2 Forest plot of hazard ratio with 95% confidence interval for radiographic progression-free survival based on BICR from subgroup analysis (Full analysis set): DCO 02-OCT-2022





Hazard ratio of [¹⁷⁷Lu]Lu-PSMA-617 vs. ARDT obtained from stratified Cox PH model.

* Prior ARDT and symptomatology subgroups are unstratified.

Stratification from the IRT data: prior ARDT use in CRPC vs. HSPC: asymptomatic or mildly symptomatic per stratification entered at randomization in IRT (score of 0-3 on item 3 of the Brief Pain inventory Short Form (BPI-SF) questionnaire vs. symptomatic (score of >3 on item 3 of the BPI-SF questionnaire)

Source: [Study B12302 IA3-Figure 14.2-1.3a]

Another supplementary analysis of rPFS based on BICR using a Cox regression model within each stratum by IRT was performed and showed results in favour of AAA617 arm with an HR ranging from 0.32 to 0.62, which was consistent with the primary analysis for rPFS [Study B12302 IA3-Table 14.2-1.2a]. However, these results should be interpreted with caution where there are a small number of patients and events.

Additionally, post-hoc sub-population analyses of asymptomatic/mildly symptomatic patients is available in [Study B12302 CSR Addendum 1] and showed a consistent rPFS benefit for the AAA617 arm, as observed for the overall population.

Updated analysis of Radiographic progression-free survival: DCO 27-Feb-2024

At the time of the third interim OS analysis There were 154 events (65.8%; 142 radiographic progression events and 12 deaths) in the AAA617 arm and 180 events (76.9%; 173 radiographic progression events and 7 deaths) in the ARPI/ARDT arm. The median rPFS was 11.60 months (95% CI: 9.30, 14.19) in the AAA617 arm vs. 5.59 months (95% CI: 4.21, 5.95) in the ARPI/ARDT arm.

The rPFS endpoint results for the following analyses based on the third interim DCO of 27- Feb-2024 showed similar results as shown in the primary analysis based on DCO of 02-Oct- 2022:

- Concordance analysis [Study B12302 IA3-Table 14.2-1.5b], [Study B12302 IA3-Table 14.2-1.6b];
- Sensitivity analysis [Study B12302 IA3-Table 14.2-1.3b];
- Supplementary analysis [Study B12302 IA3-Table 14.2-1.7b], [Study B12302 IA3-Table 14.2-1.2b], [Study B12302 IA3-Table 14.2-1.8b));
- Subgroup analysis [Study B12302 IA3-Table 14.2-1.4b].

Table 3-9 Analysis of radiographic progression-free survival based on independent central review using Kaplan Meier method (Full analysis set): DCO 27-Feb-2024

	[177Lu]Lu-PSMA-617 N=234	ARDT N=234
Number of events - n(%)	154 (65.8)	180 (76.9)
Radiographic progression	142 (60.7)	173 (73.9)
Death [1]	12 (5.1)	7 (3.0)
Number censored - n(%)	80 (34.2)	54 (23.1)
Ongoing without event [2]	42 (17.9)	19 (8.1)
Adequate assessment no longer available [3]	19 (8.1)	8 (3.4)
Withdrew consent	4 (1.7)	3 (1.3)
Event documented after two or more missing tumour assessments	15 (6.4)	24 (10.3)
Lost to follow-up [4]	0	0
Hazard ratio (95% CI) [177Lu]Lu-PSMA-617 vs ARDT [5]	0.49 [0.39, 0.61]	
Percentiles (95% CI)		
25 th	5.72 [4.01, 6.08]	2.30 [2.14, 2.69]
50 th (Median)	11.60 [9.30, 14.19]	5.59 [4.21, 5.95]
75 th	19.75 [17.38, 25.82]	10.91 [8.38, 12.22]
Kaplan-Meier estimates (%) (95% CI)		
3 months	84.5 [79.0, 88.7]	68.5 [61.9, 74.2]
6 months	71.5 [65.0, 77.1]	40.9 [34.2, 47.5]
9 months	58.0 [51.1, 64.3]	25.8 [20.0, 32.1]

	[177Lu]Lu-PSMA-617 N=234	ARDT N=234
12 months	48.4 [41.4, 55.0]	19.7 [14.4, 25.6]

NE: not estimable.

[1] Death without radiographic progression.

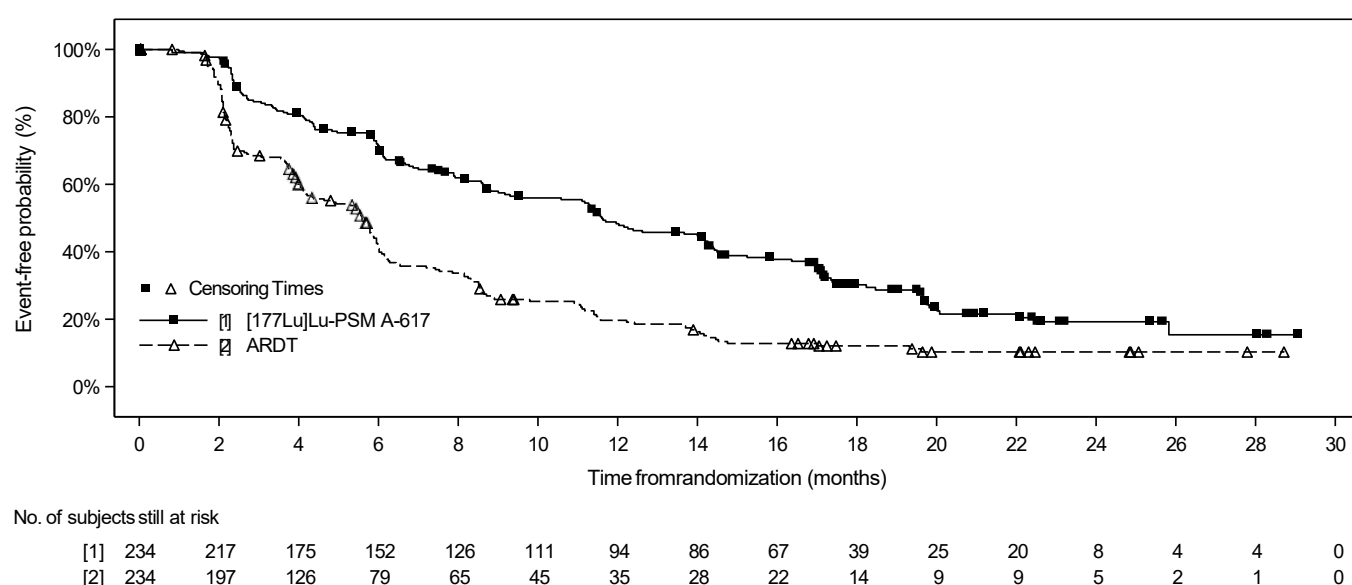
[2] Patients without event and had adequate follow-up as of data cut-off.

[3] Patients censored without adequate evaluations for a specified period prior to data cut-off or without adequate baseline assessment.

[4] Recorded on the End of treatment or End of post-treatment follow-up disposition CRF.

[5] Hazard ratio obtained from stratified Cox PH model. Stratification factors from IRT data : prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic per IRT (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score >3 on item 3 of the BPI-SF questionnaire). Source: [Study B12302 IA3-Table 14.2-1.1b]

Figure 3-3 Kaplan-Meier plot of radiographic progression-free survival based on independent central review (Full analysis set): DCO 27-Feb-2024



Source: [Study B12302 IA3-Figure 14.2-1.1b]

5.2.8.2. Key secondary efficacy endpoint results: Overall survival

Overall survival at first, second and third interim analyses

At the time of the primary rPFS analysis based on the DCO of 02-Oct-2022, the first interim OS analysis was based on an information fraction (IF) of 13.5%. The pre-specified Lan-DeMets (O'Brien-Fleming) efficacy boundary for statistical significance was not crossed [Study B12302 IA3-Section 11.2.1].

At the time of the secondary interim OS analysis based on the DCO of 21-Jun-2023, the analysis of OS was based on an IF of 45.1%. The pre-specified Lan-DeMets (O'Brien-Fleming) efficacy boundary for statistical significance was not crossed [Study B12302 IA3-Section 11.2.1].

The third interim analysis (DCO 27-Feb-2024) of OS was based on 216 deaths corresponding to a 72.7% IF (of the targeted 297 events for the final OS analysis) with DCO of 27-Feb-2024. The pre-specified Lan-DeMets (O'Brien-Fleming) efficacy boundary for statistical significance was not crossed [Study B12302 IA3-Section 11.2].

Overall survival at final analysis: DCO 01-Jan-2025

The study did not meet its key secondary endpoint of overall survival.

The final OS analysis (DCO date of 01-Jan-2025) was based on 299 deaths (~100% information fraction) and the HR (95% CI) for OS was 0.91 (0.72, 1.14) and one-sided p-value was 0.20. ([Table 3-10](#)).

There were 142 events (60.7%) in the AAA617 arm and 157 events (67.1%) in the ARPI/ARDT arm. The median OS (95% CI) was 24.48 months (19.55, 28.94) and 23.13 months (19.61, 25.53), respectively ([Table 3-10](#)). K-M plot for overall survival is presented in [Figure 3-4](#).

OS analysis was conducted without adjusting for crossover following the ITT principle.

Table 3-10 Overall survival unadjusted for crossover (Full Analysis Set): DCO 01-Jan-2025

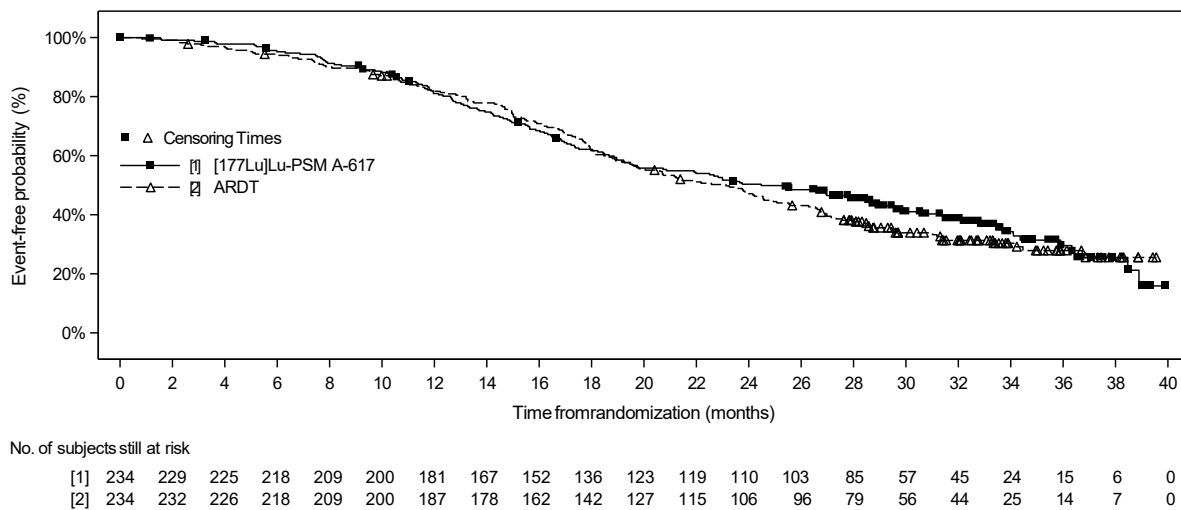
	[177Lu]Lu-PSMA-617 N=234	ARDT N=234
Number of events - n(%)	142 (60.7)	157 (67.1)
Number censored - n(%)	92 (39.3)	77 (32.9)
Hazard ratio (95% CI) [177Lu]Lu-PSMA-617 vs ARDT [1]	0.91 [0.72, 1.14]	
P-value [177Lu]Lu-PSMA-617 vs ARDT [2]	0.20	
Percentiles (95% CI)		
25 th	13.93 [12.16,	14.95 [12.81,
	15.64]	16.56]
50 th (Median)	24.48 [19.55,	23.13 [19.61,
	28.94]	25.53]
75 th	38.47 [34.37, NE]	NE [33.35, NE]
K-M estimates (%) (95% CI)		
6 months	95.2 [91.5, 97.3]	94.0 [90.1, 96.4]
12 months	81.1 [75.4, 85.6]	81.8 [76.2, 86.2]
18 months	61.7 [55.0, 67.7]	62.1 [55.5, 68.1]
24 months	50.4 [43.6, 56.7]	47.2 [40.6, 53.5]
30 months	41.1 [34.3, 47.7]	33.9 [27.7, 40.2]
36 months	29.6 [21.8, 37.8]	27.9 [21.4, 34.8]
42 months	NE [NE, NE]	NE [NE, NE]

NE: not estimable.

[1] Hazard ratio obtained from stratified Cox PH model.

[2] One-sided p-value obtained from stratified log-rank test. Stratification factors from IRT data : prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic (score of 0-3 on item 3 of the BPI-SF questionnaire) vs symptomatic (score >3 on item 3 of the BPI-SF questionnaire). Source: [Study B12302 IA4-Table 14.2-2.1]

Figure 3-4 K-M plot of overall survival (Full Analysis Set): DCO 01-Jan-2025



Source: [Study B12302 IA4- Figure 14.2-2.1]

Supplementary IPCW analysis of OS

In order to further assess the impact of crossover on OS, Inverse Probability of Censoring Weighting (IPCW) was applied to estimate a crossover adjusted HR to compare the true treatment effect between AAA617 and ARPI/ARDT without a crossover confounding using a weighted Cox proportional hazards model where the weights assigned to each patient were estimated according to pre-specified baseline and time-dependent characteristics (covariates). Candidate covariates were determined as potentially influencing crossover; the following factors were selected prior to the database lock and included into the statistical models:

- Baseline factors (categorical): age, stage at diagnosis, prior ARPI/ARDT medication, prior radiation, liver metastases, bone involvement, PSA level, initial Gleason score, lactate dehydrogenase, alkaline phosphatase, hemoglobin and the two stratification factors.
- Baseline factors (continuous): lymphocyte count, neutrophil count and time since prostate cancer diagnosis.
- On-treatment time dependent factors: time to rPD as per BICR and ECOG performance status.

The full model was used for the main analysis including all covariates in the weight calculation and for the estimation of the adjusted treatment effect in the multivariate weighted Cox model. The statistical analyses were performed using the R-package IPCW switch ([Grafféo et al 2019](#)).

An IPCW analysis identified and estimated an OS benefit that otherwise would not have been detected using an unadjusted ITT or RPSFT analysis.

IPCW assumes there are no unmeasured confounders. While this assumption cannot be verified, evaluating measured covariates and findings from other studies in similar disease areas, along with selecting these covariates based on clinical relevance, may support the appropriateness of this assumption [Study B12302 IA4-Section 3.2.2].

The full model resulted in a HR = 0.59 (95% CI: 0.38, 0.91) when randomisation factors were treated as strata, and a HR = 0.59 (95% CI: 0.37, 0.94) when randomisation factors were treated as

covariates. Additional sensitivity analyses were performed on subsets of the candidate covariates. Overall, across all models, results adjusting for crossover using IPCW indicated a survival benefit for AAA617, with a crossover-adjusted HR ranging from 0.54 to 0.62 ([Table 3-11](#)).

Table 3-11 Crossover corrected OS analyses by Inverse Probability Censoring Weighting (IPCW): DCO 01-Jan-2025 Model

Variable	1	2	3§	4	5	6	7§	8
Age			•				•	
Stage at diagnosis			•	•			•	
Prior ARDT medication			•				•	
Prior radiation			•	•			•	
Liver metastases			•				•	
Bone involvement			•				•	
PSA level			•				•	
Initial Gleason score			•				•	
LDH			•				•	
Alkaline phosphatase			•	•	•		•	•
Hemoglobin			•	•	•		•	•
Lymphocyte count			•				•	
Neutrophile count			•				•	
Time since prostate cancer diagnosis			•	•	•		•	•
rPD as per BICR**	•	•	•	•	•	•	•	•
ECOG**	•	•	•	•	•	•	•	•
Prior ARDT use (cancer type)#		•	•	•	•	•	•	•
Symptomatology#		•	•	•	•	•	•	•
Randomised treatment##	•	•	•	•	•	•	•	•
HR	0.56	0.54	0.59	0.60	0.60	0.55	0.59	0.62
95% CI	0.35-	0.32-	0.37-	0.37-	0.38-	0.36-	0.38-	0.42-
	0.88	0.89	0.94	0.96	0.96	0.85	0.91	0.94
AIC	4899	2829	2494	2392	2566	2258	1949	2017

-The dot marks covariates used for weight estimation and included in the weighted Cox model # either used as stratification factor (models 6-8) or as covariate (models 1-5)

not used for weight estimation, treatment variable and the two time-dependent factors (**) are included in all weighted Cox regression models

-HR = hazard ratio of AAA617 vs ARDT from weighted Cox model

-AIC = Akaike information criterion; measures model fit incl. penalty term for each variable included in the model; smaller values indicate better fit of weighted Cox model

-The two stratification factors (prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic vs symptomatic patient) were used:

as additional covariate in models 1-5 or as strata in models 6-8.

§ FuII model including all covariates are model 3 in i) and model 7 in ii) Source: [Study B12302 IA4-Table 14.2-2.15]

Supplementary RPSFT analysis of OS

The RPSFT analysis yielded an estimated $\psi = -0.41$ corresponding to an estimated prolongation of overall survival by a multiplicative factor of $\exp(0.41) = 1.5$ if purely treated with AAA617 versus never treated with AAA617. Transferring these results to a HR scale yields a crossover adjusted HR of 0.84 (95% CI: 0.55, 1.28). The median OS was 24.5 months (95% CI: 19.6, 28.9) in the AAA617 arm and 21.6 months (95% CI: 18.6, 24.5) in the reconstructed (i.e. as if no cross-over was allowed) ARPI/ARDT arm. The RPSFT model maintains the ITT analysis p value, widening the confidence interval [Study B12302 IA4-Table 14.2-2.5], [Study B12302 IA4- Figure 14.2-2.3], and [Study B12302 IA4- Figure 14.2-2.2].

The RPSFT model assumes that the treatment effect of AAA617 administered to a patient is the same, regardless of when the treatment was administered (i.e. at time of randomisation vs. at time of crossover). With insufficient data to support that the treatment effect of AAA617 is the same in an earlier line vs. post radiographic progression, the essential assumption for use of the RPSFT model may not be met. Another limitation of the RPSFT method is that it cannot adjust for confounding in the context of overlapping ITT survival curves ([Watkins et al 2013](#)). IPCW is thus considered a more appropriate model to adjust for crossover in Study B12302.

5.2.8.3. PFS2: DCO 27-Feb-2024

PFS2 was defined as time from date of randomisation to the first documented progression by investigator's assessment (radiographic progression, clinical progression, PSA progression) or death from any cause, whichever occurred first on next-line therapy.

Next-line therapy was defined as the first new (systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of reason for end of treatment. For patients in the ARPI/ARDT arm who crossed over, treatment with AAA617 treatment was considered the next-line therapy.

There were 119 PFS2 events reported in the AAA617 arm, consisting of 53 progressions and 66 deaths, and 121 PFS2 events reported in the ARPI/ARDT arm, consisting of 75 progressions and 46 deaths [Study B12302 IA3-Table 14.2-5.1 and Figure 14.2-5.1].

The censoring rate was comparable in both treatment arms (AAA617 arm: 49.1%; ARPI/ARDT arm: 48.3%). The K-M plot showed trends in favour of the AAA617 arm. The estimated PFS2 event free probability at 12 months was 74.0% (95% CI: 67.7, 79.3) in the AAA617 arm and 64.2% (95% CI: 57.3, 70.3) in the ARPI/ARDT arm [Study B12302 IA3-Table 14.2-5.1 and Figure 14.2-5.1].

The median PFS2 was 18.00 months (95% CI: 15.70, 20.53) in the AAA617 arm and 15.31 months (95% CI: 13.37, 20.21) in the ARPI/ARDT arm.

rPFS2 for Crossover Analysis Set: DCO: 27-Feb-2024

rPFS2 by BICR was defined for the Crossover Analysis Set as the time from start of crossover treatment with AAA617 to date of radiographic disease progression by BICR or death from any cause [Study B12302 IA3-Section 11.3.1.1].

A total of 134 of 234 patients randomised to the ARPI/ARDT arm crossed over to receive AAA617 at the IA3. There were 86 rPFS2 events (64.2%) reported for those 134 crossover patients that included 78 radiographic progressions and 8 deaths. The median time to rPFS2 was 5.42 months (95% CI: 3.65, 5.91) from the start of crossover treatment to the date of radiographic disease progression by BICR or death. A total of 48 patients (35.8%) were censored, mainly due to being "ongoing without event" (31 patients, 23.1%) [Study B12302 IA3-Table 14.2-3.1].

5.2.8.4. PSA50 response: DCO 27-Feb-2024

PSA50 response was defined as the proportion of patients who achieved a $\geq 50\%$ decrease in their PSA from baseline at any time during the randomised treatment confirmed by a second PSA measurement ≥ 4 weeks [Study B12302 IA3-Section 11.3.1.4].

Table 3-12 PSA50 response (Full analysis set): DCO 27-Feb-2024

	[177Lu]Lu-PSMA-617 N=234		ARDT N=234	
	n/m (%)	95% CI	n/m (%)	95% CI
PSA50 response rate*	113/220 (51.4)	(44.6, 58.1)	39/226 (17.3)	(12.6, 22.8)
Week 12	71/170 (41.8)	(34.3, 49.6)	25/182 (13.7)	(9.1, 19.6)
Week 24	77/142 (54.2)	(45.7, 62.6)	20/125 (16.0)	(10.1, 23.6)
Week 48	1/45 (2.2)	(0.1, 11.8)	7/47 (14.9)	(6.2, 28.3)

Week 12, 24 and 48 include any PSA measurements at the corresponding timepoint ± 2 weeks. n : number of patients with a PSA50 response at the corresponding week.

m : number of patients with a PSA measurement at the corresponding week. Percentages are based on m.

* means PSA50 response at any time during randomised treatment.

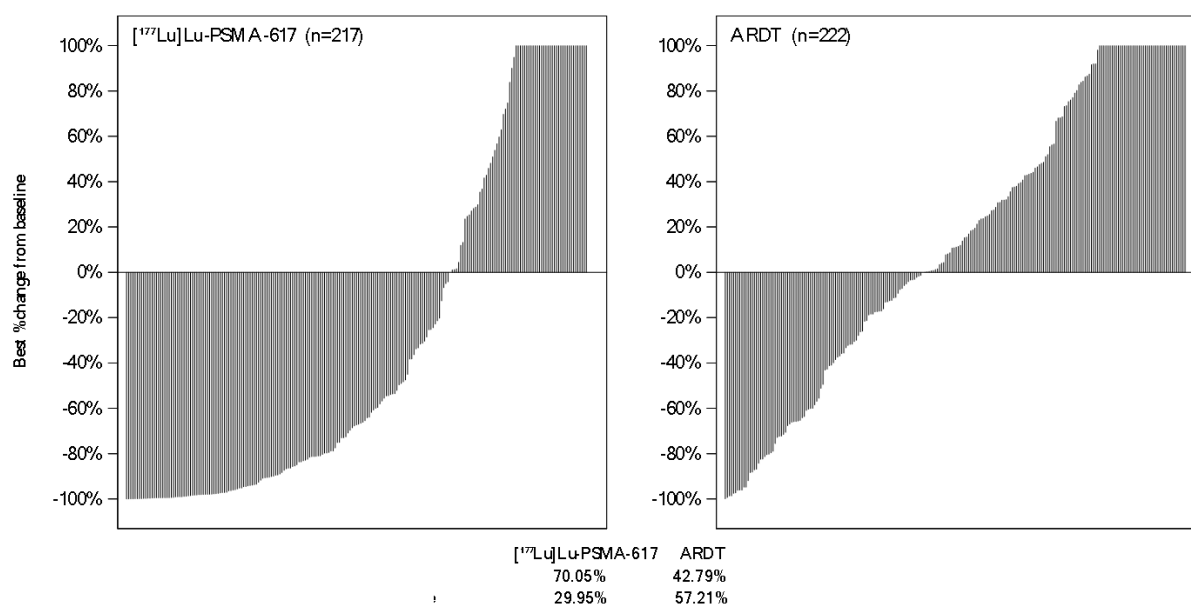
Any data post further antineoplastic therapy (including crossover) is excluded from the analysis. Source: [Study B12302 IA3-Table 14.2-9.1]

5.2.8.5. Time to PSA progression: DCO 27-Feb-2024

TTPSAP was defined as time from randomisation to the date of 1) $\geq 25\%$ increase and ≥ 2 ng/mL above the nadir, confirmed by a second value ≥ 3 weeks later if there was PSA decline from baseline, or 2) $\geq 25\%$ increase and ≥ 2 ng/mL increase from baseline beyond 12 weeks if there was no PSA decline from baseline [Study B12302 IA3-Section 11.4.3].

There was a 60% risk reduction in TTPSAP in favour of the AAA617 arm (HR: 0.40, 95% CI 0.31, 0.50). The median TTPSAP was 10.64 months (95% CI: 8.57, 12.68) for the AAA617 arm vs. 4.24 months (95% CI: 3.48, 4.44) for the ARPI/ARDT arm [Study B12302 IA3-Table 14.2-9.2].

Figure 11-8 Waterfall plot for best percentage change from baseline in maximum decline in PSA (FAS)



Decrease in best percentage change from baseline. Increase/zero changes in best percentage change from baseline.
n – Participants with a value at both baseline and post-baseline. Percentages are based on 'n'.
Increase ≥100% have been set to 100%.
Data cut-off date: 27-Feb-2024
Source: Figure 14.2-9.1

5.2.8.6. Time to symptomatic skeletal events TTSSE): DCO 27-Feb-2024

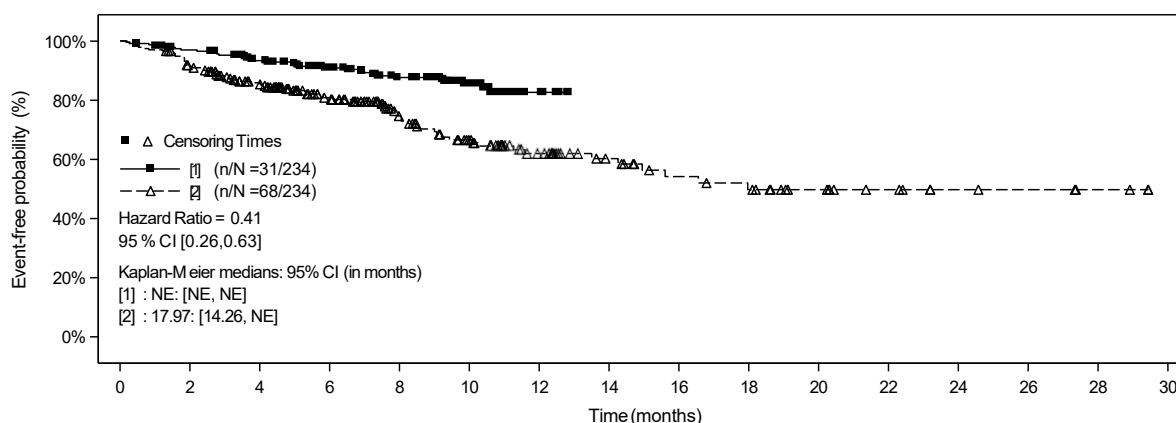
TTSSE was defined as date of randomisation to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumour-related orthopaedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause (whichever occurred first) [Study B12302 IA3-Section 11.3.1.5]. TTSSE was assessed only during the study treatment period.

A clinically meaningful benefit in TTSSE was observed in favour of the AAA617 arm with a HR = 0.41 (95% CI: 0.26, 0.63) and an estimated 59% reduction in risk of SSE (Figure 3-5, [Study B12302 IA3-Table 14.2-6.1]). Nevertheless, the results need to be interpreted in light of the “while on-treatment” estimand. There were 31 events (13.2%; 27 SSE events and 4 deaths) in the AAA617 arm and 68 events (29.1%; 63 SSE events and 5 deaths) in the ARPI/ARDT arm.

The median time to SSE was not reached in the AAA617 arm and was 17.97 (95% CI: 14.26, NE) in the ARPI/ARDT arm. The rate of censoring was higher in the AAA617 arm than the ARPI/ARDT arm (86.8% vs. 70.9%).

A benefit in TTSSE excluding events of death was observed in favour of the AAA617 arm with a HR = 0.38 (95% CI: 0.24, 0.61) indicating an estimated 62% reduction in risk of TTSSE [Study B12302 IA3-Table 14.2-6.2 and Figure 14.2-6.2]. There were 27 events (11.5%) in the AAA617 arm vs. 63 events (26.9%) in the ARPI/ARDT arm; the median time to event was not reached in either treatment arm.

Figure 3-5 Time to symptomatic skeletal event using the Kaplan-Meier method (Full Analysis Set): DCO 27-Feb-2024



No. of subjects still at risk

[1]	234	220	201	173	156	89	6	0	0	0	0	0	0	0	0	0
[2]	234	210	173	130	87	66	46	33	25	22	15	10	6	5	3	0

[1] : [177Lu]Lu-PSMA-617, [2] : ARDT.

Hazard ratio of [177Lu]Lu-PSMA-617 vs ARDT obtained from stratified Cox PH model.

Stratification factors from IRT data: prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score >3 on item 3 of the BPI-SF questionnaire).

Source: [Study B12302 IA3-Figure 14.2-6.1]

5.2.8.7. Time to soft tissue progression: DCO 27-Feb-2024

TTSTP was defined as time from randomisation to radiographic soft tissue progression per PCWG3-modified RECIST v1.1 assessed by BICR. This analysis is based on the RECIST analysis set and includes FAS participants with evaluable soft tissue disease by PCWG3-modified RECIST v1.1 at baseline. It is therefore not a randomised comparison [Study B12302 IA3-Section 11.3.1.6].

The HR was 0.34 (95% CI: 0.23, 0.51) in the AAA617 arm compared to the ARPI/ARDT arm, indicating a 66% reduction in the risk of soft tissue progression [Study B12302 IA3-Table 14.2-7.1 and Figure 14.2-7.1].

The number of events was lower in the AAA617 arm (47 events, 45.2%) than the ARPI/ARDT arm (63 events, 61.8%). The median TTSTP was longer in the AAA617 arm (19.65 months, 95% CI: 14.49, NE) compared to the ARPI/ARDT arm (5.95 months, 95% CI: 3.98, 8.54). The estimated STP event free probability at 12 months was 67.1% (95% CI: 56.7, 75.5) in the AAA617 arm and 28.5% (95% CI: 18.2, 39.8) in the ARPI/ARDT arm.

5.2.8.8. Time to chemotherapy: DCO 27-Feb-2024

Time to chemotherapy (TTCT) was defined as time from randomisation to initiation of the first subsequent antineoplastic therapy (excluding crossover AAA617) or death, whichever occurred first.

The number of TTCT events (first subsequent therapy requirement and deaths), as assessed using the K-M method, was comparable between the AAA617 and ARPI/ARDT arms (152 events, 65.0% vs. 148 events, 63.2%); the ITT-based HR was 1.07 (95% CI: 0.86, 1.35). The median TTCT was 15.6 months in the AAA617 arm and 15.9 months in the ARPI/ARDT arm

5.2.8.9. Patient reported outcomes: DCO 27-Feb-2024

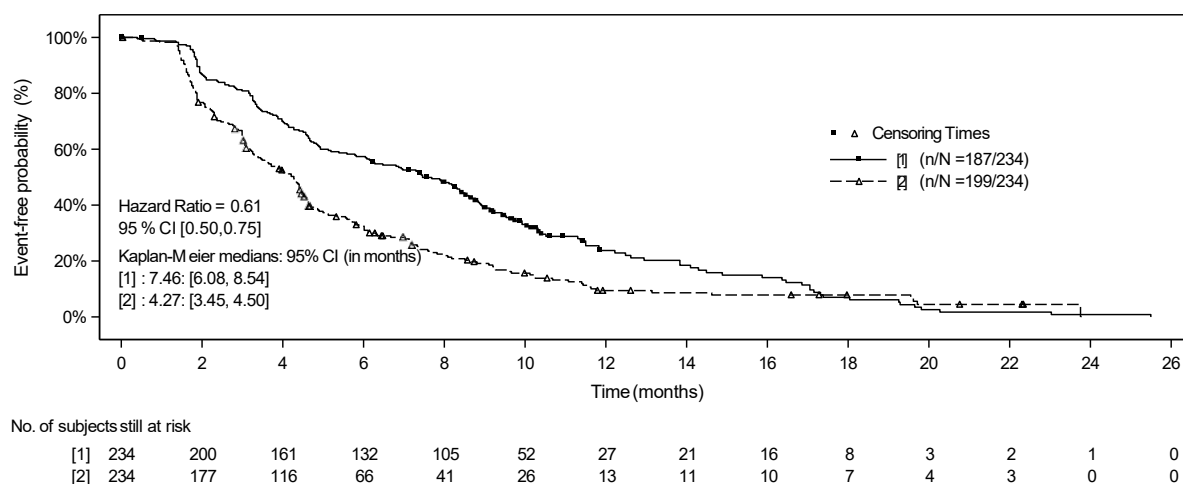
5.2.8.9.1. FACT-P : DCO 27-Feb-2024

Patients in the AAA617 arm had a lower risk of deterioration of FACT-P total score and all FACT-P subscales compared to the ARPI/ARDT arm.

Time to deterioration in FACT-P total score or disease progression or death is the pre-specified secondary endpoint, and using 10 points as the worsening threshold, the Kaplan-Meier method showed a 39% reduction in risk (HR = 0.61 with 95% CI: 0.50, 0.75) (Figure 3-6). Overall, AAA617 patients had over a 3-month prolongation in median time to significant worsening of FACT-P total score. In addition, the mean change from baseline in FACT-P total score demonstrated relatively stable HRQoL in patients treated with AAA617 and declining HRQoL in the ARPI/ARDT patients (Figure 3-7).

Similar trends were observed for other total scores and subscales (Table 3-13). Mean change from baseline for FACT-P total score for FAS demonstrated relatively stable HRQoL in patients treated with AAA617 and declining HRQoL in the ARPI/ARDT arm patients [SCE Appendix 1-Figure 1-5].

Figure 3-6 Kaplan-Meier plot of time to worsening for FACT-P total score (Full analysis set): DCO:27-Feb-2024



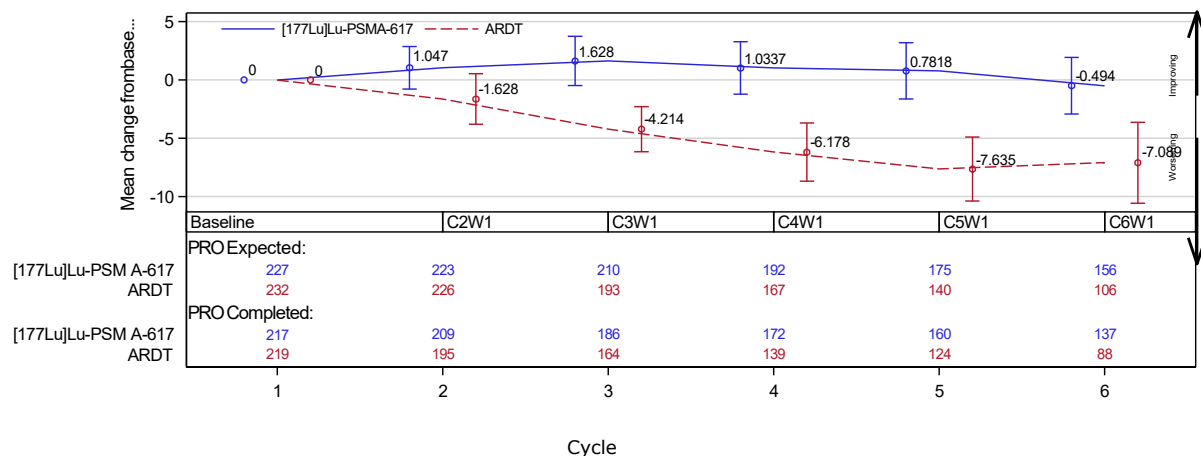
[1]: [177Lu]Lu-PSMA-617, [2]: ARDT.

Hazard ratio of [177Lu]Lu-PSMA-617 vs ARDT obtained from stratified Cox PH model. Stratification factors from IRT data : prior ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score >3 on item 3 of the BPI-SF questionnaire).

PRO worsening events were considered till end of randomised treatment period, and clinical disease progression and deaths were considered before crossover.

Source: [Study B12302 IA3-Figure 14.2-11.1]

Figure 3-7 Change from baseline for FACT-P total score (Full analysis set): DCO:27-Feb-2024



PRO expected includes participants who both completed and did not complete the PRO measure, e.g. the participant did not attend an onsite visit, the participant did not complete the PRO measure at the attended onsite visit, at each planned cycle.

Source: [SCE Appendix 1–Figure 1-5]

Table 3-13 Summary of time to worsening analyses of FACT-P scores (Full analysis set): DCO 27-Feb-2024

	HR# (95% CI)	Median time to worsening in months (95% CI)	
		AAA617	ARPI/ARDT
Prostate cancer subscale	0.56 (0.46, 0.69)	6.14 (4.90, 7.59)	3.55 (3.09, 4.34)
Pain-related subscale	0.64 (0.52, 0.78)	5.91 (4.86, 6.93)	3.61 (3.15, 4.34)
Physical well-being subscale	0.60 (0.49, 0.73)	7.20 (5.85, 8.25)	3.71 (3.25, 4.37)
Social/family well-being subscale	0.88 (0.72, 1.08)	5.19 (4.57, 6.87)	4.37 (3.71, 5.78)
Emotional well-being subscale	0.72 (0.59, 0.89)	8.54 (7.33, 9.46)	4.63 (4.11, 5.59)
Functional well-being subscale	0.81 (0.66, 0.98)	5.19 (4.67, 6.77)	4.40 (3.81, 4.67)
FACT-P total score	0.61 (0.50, 0.75)	7.46 (6.08, 8.54)	4.27 (3.45, 4.50)
FACT-P Trial Outcome Index score	0.66 (0.53, 0.80)	7.46 (6.21, 8.87)	4.40 (3.71, 4.80)
FACT Advanced Prostate Symptom Index (FAPSI) 8 score	0.53 (0.43, 0.65)	7.39 (6.05, 8.51)	3.65 (3.19, 4.37)
FACT-G total score	0.72 (0.59, 0.89)	7.52 (6.08, 8.77)	4.40 (3.98, 4.93)

Hazard ratio obtained from stratified Cox PH model. Stratification factors from IRT data: prior ARDT use in CRPC vs. HSPC; asymptomatic or mildly symptomatic (score of 0-3 on item 3 of the BPI-SF questionnaire) vs. symptomatic (score > 3 on item 3 of the BPI-SF questionnaire).

PRO worsening events were considered till end of randomised treatment period, and clinical disease progression and deaths were considered before crossover.

Source: [Study B12302 IA3-Table 14.2-11.1]

5.2.8.9.2. EQ-5D-5L: DCO 27-Feb-2024

Time to worsening in EQ-5D-5L utility score was longer in the AAA617 arm than the ARPI/ARDT arm (HR: 0.67; 95% CI: 0.54, 0.82). The median time to worsening was 6.28 months (95% CI: 4.70, 7.89) in the AAA617 arm vs. 3.88 months (95% CI: 3.25, 4.44) in the ARPI/ARDT arm [Study B12302 IA3-Table 14.2-10.1]. EQ-5D-5L VAS scores were generally stable over time in both treatment arms [Study B12302 IA3-Table 14.2-10.2].

5.2.8.9.3. BPI-SF: DCO 27-Feb-2024

Summary of BPI-SF scales is presented in [Table 3-14](#). Time to worsening in BPI-SF pain intensity scale (earliest occurrence of $\geq 30\%$ increase or ≥ 2 point increase relative to baseline, clinical progressive disease, or death) is presented in [Figure 3-8](#). Time to worsening in pain intensity scale was delayed in the AAA617 arm (HR: 0.72; 95% CI: 0.59, 0.88). The median time to worsening in pain intensity scale was 5.03 months (95% CI: 4.40, 6.80) in the AAA617 arm and 3.65 months (95% CI: 3.09, 4.37) in the ARPI/ARDT arm ([Table 3-14](#)).

Table 3-14 Summary of time to worsening analyses of BPI-SF scales (Full analysis set): DCO 27-Feb-2024

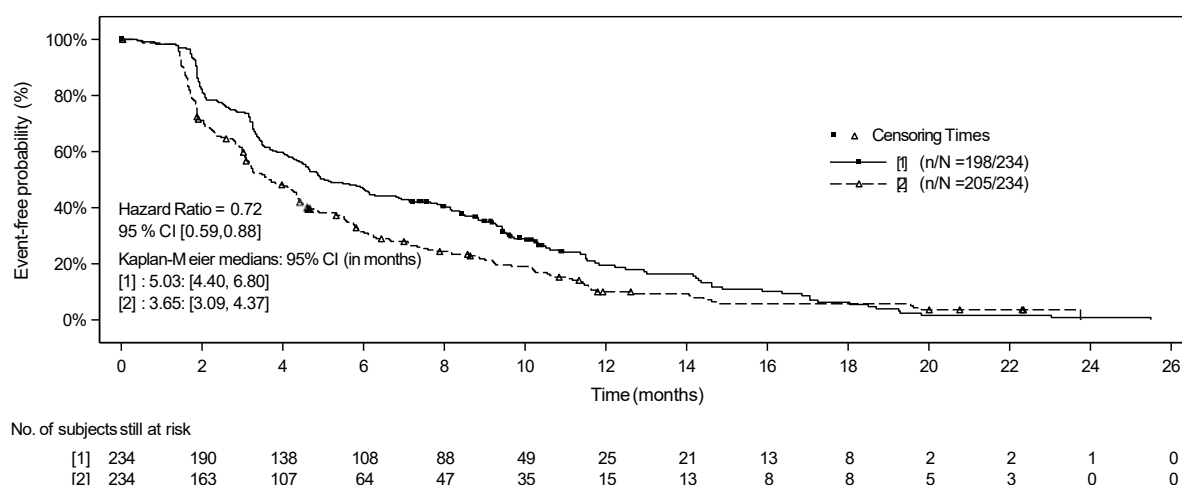
Score	HR# (95% CI)	Median time to worsening in months (95% CI)	
		AAA617	ARPI/ARDT
Disease-related pain	0.73 (0.59, 0.88)	5.13 (4.11, 6.14)	3.65 (3.06, 4.34)
Pain intensity scale	0.72 (0.59, 0.88)	5.03 (4.40, 6.80)	3.65 (3.09, 4.37)
Pain interference scale	0.74 (0.61, 0.91)	5.82 (4.57, 7.03)	3.71 (3.06, 4.40)

Hazard ratio obtained from stratified Cox PH model. Stratification factors from IRT data: prior ARDT use in CRPC vs. HSPC; asymptomatic or mildly symptomatic (score of 0-3 on item 3 of the BPI-SF questionnaire) vs. symptomatic (score > 3 on item 3 of the BPI-SF questionnaire).

PRO worsening events were considered till end of randomised treatment period, and clinical disease progression and deaths were considered before crossover.

Source: [Study B12302 IA3-Table 14.2-12.1]

Figure 3-8 Kaplan-Meier Plot of Time to Worsening for BPI-SF pain intensity scale (Full Analysis Set): DCO 27 Feb 2024



Hazard ratio of [177Lu]Lu-PSMA-617 vs ARDT obtained from stratified Cox PH model. Stratification factors from IRT data : prior ARPI/ARDT use in CRPC vs HSPC; asymptomatic and mildly symptomatic (score of 0-3 on item 3 of the Brief Pain Inventory Short Form (BPI-SF) questionnaire) vs symptomatic (score > 3 on item 3 of the BPI-SF questionnaire).

PRO worsening events were considered till end of randomised treatment period, and clinical disease progression and deaths were considered before crossover.

Source: [Study B12302 IA3- Figure 14.2-12.1]

5.2.8.10. Explorative Endpoints

5.2.8.10.1. Overall response rate and disease control rate: DCO 27-Feb-2024

Overall response rate (ORR) and disease control rate (DCR) data are presented in [Study B12302 IA3-Section 11.4.1]. ORR was defined as the proportion of patients with BOR of CR or PR by BICR according to RECIST v1.1. ORR was evaluated for the RAS (see [Section 1.2.2.1](#) for definition of RAS).

5.2.8.10.2. ORR considering both soft tissue and bone disease

For patients with measurable disease at baseline (i.e. at least one target lesion in soft tissue at baseline) the ORR accounting for both soft tissue and bone disease was 48.6% (95% CI: 36.7, 60.7) in the AAA617 arm (20.8% patients with CR and 27.8% patients with PR) vs. 13.9% (95% CI: 6.9, 24.1) in the ARPI/ARDT arm (2.8% patients with CR and 11.1% patients with PR) ([Table 3-15](#)). The DCR was 77.8% in the AAA617 arm vs. 55.6% in the ARPI/ARDT arm.

Table 3-15 Best overall radiological response accounting for soft tissue and bone disease based on BICR (RECIST analysis set - patients with measurable disease at baseline): DCO 27-Feb-2024

	[177Lu]Lu-PSMA-617 N=72 n (%)	ARDT N=72 n (%)
Patient with measurable disease at baseline	72 (100)	72 (100)
Best overall response		
Complete response (CR)	15 (20.8)	2 (2.8)
Partial response (PR)	20 (27.8)	8 (11.1)
Stable disease (SD)	21 (29.2)	30 (41.7)
Progressive disease (PD)	14 (19.4)	27 (37.5)
Unknown (UNK)	2 (2.8)	5 (6.9)
Overall response rate (ORR: CR+PR)	35 (48.6)	10 (13.9)
95% CI	(36.7, 60.7)	(6.9, 24.1)
Disease control rate (DCR: CR+PR+SD)	56 (77.8)	40 (55.6)
95% CI	(66.4, 86.7)	(43.4, 67.3)

Responses are based on soft tissue and bone lesion assessment. BOR=PD also accounts for bone progression
Source: [Study B12302 IA3-Table 14.2-13.4]

5.2.8.10.3. Duration of response: DCO 27-Feb-2024

Duration of radiological soft tissue response was defined as the time between the date of first documented BOR (CR or PR), according to PCWG3-modified RECIST v1.1 assessed by BICR, and the date of first documented soft tissue progression or death due to any cause [Study B12302 IA3-Section 11.4.2].

The median DOR in the RAS accounting for patients with measurable disease at baseline was not estimable for the AAA617 arm and 10.05 months (95% CI: 4.63, NE) for the ARPI/ARDT arm. At 12 months, the DOR probability was 78.6% (95% CI: 60.3, 89.2) for the AAA617 arm vs. 31.3% (95% CI: 1.5, 72.3) for the ARPI/ARDT arm [Study B12302 IA3-Table 14.2-14.3]. These results should be interpreted with caution as the analyses are limited by the low numbers of patients at risk (AAA617 arm: 12 of 36 patients, 33.3%; ARPI/ARDT arm: 4 of 11 patients, 36.4%).

5.2.8.10.4. Time to response: DCO 27-Feb-2024

Time to radiological soft tissue response per BICR using K-M method in RAS was conducted in patients with a CR or PR (43 of 104 patients, 41.3% in the AAA617 arm vs. 14 of 102 patients, 13.7% in the ARPI/ARDT arm) [Study B12302 IA3-Table 14.2-15.1].

The analysis was limited due to the low number of events. The median time to radiological soft tissue response was not reached in either arm [Study B12302 IA3-Table 14.2-15.1]. The median time to radiological response accounting for soft tissue and bone disease was not reached in both arms [Study B12302 IA3-Table 14.2-15.2].

5.2.9. Ancillary analyses

Not applicable.

5.2.10. Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial CAAA617B12302 (PSMAfore-Trial)

Study identifier	EudraCT No. 2020-003969-19; NCT04689828	
Design	Study B12302 is an open-label, multicenter, randomised study for PSMA-positive mCRPC patients previously treated with an ARPI/ARDT for whom it was considered appropriate to delay taxane-based chemotherapy. The study evaluated the superiority of AAA617 over a change of ARPI/ARDT treatment in prolonging rPFS. Only patients with PSMA-positive cancer were randomised in the study provided all other eligibility criteria were met. Enrolled patients were ≥ 18 years of age, had no prior taxane-containing regimen for progressive CRPC or hormone-sensitive prostate cancer (HSPC), and had a gallium (68Ga) gozetotide positron emission tomography (PET)/computed tomography (CT) scan assessed for eligibility by a central reader. Patients had mCRPC and progressed only once on a prior second-generation ARPI/ARDT (abiraterone acetate, enzalutamide, darolutamide or apalutamide) as their most recent therapy. Patients had mCRPC and progressed only once on a prior second-generation ARPI/ARDT (abiraterone acetate, enzalutamide, darolutamide or apalutamide) as their most recent therapy. Only patients with PSMA-positive cancer were randomised in the study provided all other eligibility criteria were met. Patients were randomised using a 1:1 ratio to receive either 7.4 GBq (200 mCi) $\pm$ 10% AAA617 once every 6 weeks (1 cycle) for 6 cycles or a change in ARPI/ARDT (abiraterone or enzalutamide). <free text>	
	Study initiation date: (first participant first visit)	15-Jun-2021
	Data cut-off dates:	02-Oct-2022 (primary analysis) 01-Januar -2025 (Final OS analysis)
Hypothesis	Superiority	
Treatments groups/ Stratification	AAA617	AAA617 was administered i.v. at a dose of 7.4 GBq (200 mCi) $\pm$ 10% AAA617 once every 6 weeks (1 cycle) for 6 cycles.

	ARDT		Change of ARPI/ARDT treatment included approved AR-axis targeted therapy abiraterone or enzalutamide. ARPI/ARDT treatment was dosed as per approved local labels and guidelines including contraceptive requirements. Abiraterone was to be dosed with prednisone or prednisolone as per the approved local labels.
	Randomisation: 1:1		Stratification: - Prior ARDT use - Symptomatology
Endpoints and definitions	Primary endpoint	Median rPFS	Radiographic progression-free survival (rPFS) based on blinded independent central review (BICR) as per Prostate Cancer Working Group 3 (PCWG3)-modified Response Evaluation Criteria in Solid Tumours 1.1 (RECIST 1.1) criteria
	Key Secondary Endpoint	Overall survival (all causes)	The final OS analysis (DCO date of 01-Jan-2025) was based on 299 deaths (~100% information fraction)
Database lock	Data cut-off dates: 02-Oct-2022 (primary analysis); 27-Feb-2024 (Interim OS analysis) 01-January-2025 (Final OS analysis)		

Results and Analysis

Analysis description	Primary Analysis: ITT				
Descriptive statistics and estimate variability	Endpoint	Dimension	AAA617 Pluvicto Experimental arm	Change in ARPI/ARDT Control arm	Comment
	Primary Endpoint: Progression free survival	Median time in months (95% CI)	9.30 (6.77, NE)	5.55 (4.04, 5.95)	HR: 0.41 (0.29, 0.56) Median difference of 3.75 months
	Key secondary endpoint Overall survival	Median time in months (95% CI)	24.48 (19.55, 28.94)	23.13 (19.61, 25.53)	HR: 0.91 (0.72, 1.14) Final Analysis: 1.January 2025
Notes	Study B12302, the primary efficacy endpoint PFS was met showing a statistically significant rPFS benefit (HR=0.41) for PSMA-positive mCRPC patients treated with AAA617 compared to ARPI change after being treated with an ARPI. Per the DCO (27-Feb 2024), the median rPFS for AAA617 doubled compared to the ARPI arm (11.6 months vs. 5.6 months). However, no statistically significant benefit for overall survival was shown. Cross-over of control arm has hampered significantly the evaluation and introduced bias which challenges the reliability of the reported outcome. Control arm treatment with change in ARPI/ARDT was inappropriate and not efficacious (probably not much better than placebo) in this setting				

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive study(ies)

For details of analysis in the initial VISION trial, pivotal for the approved indication in the post-chemotherapy mCRPC population please refer to the assessment reports of the initial procedure.

5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In this procedure an extension of the indication is requested for the following indication:

“Pluvicto is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI) therapy and for whom chemotherapy is not yet clinically indicated (see section 5.1).”

Study design

The pivotal study is Study CAAA617B12302 (also referred as PSMAfore or Study B12302; [Morris et al. Lancet Oncol. 2024](#); [Fizazi et al. Ann Oncol. 2025](#)). This is a phase III open-label, randomized study in which patients were randomized (1:1) between lutetium (¹⁷⁷Lu) vipivotide tetraxetan (also referred to as ¹⁷⁷Lu-PSMA-617) and a change in ARPI (the control arm is also referred to as ARPI/ARDT). The randomized design is supported in this setting. The open-label design can be understood due to radiation protection protocols, but this design hampers interpretation of endpoints such as HR QoL. The randomization was stratified by initial prior ARPI use in CRPC vs. HSPC setting and symptomatology based on item 3 of the BPI-SF questionnaire. This is considered acceptable.

After radiographic progression patients in the ARPI arm were allowed to crossover to ¹⁷⁷Lu-PSMA-617. This is not supported, as it will hamper interpretation of OS data (refer to below). Moreover, treatment with ¹⁷⁷Lu-PSMA-617 in taxane-naïve patients is not an approved indication ([Pluvicto SmPC](#)).

Patient population

The study population included adult mCRPC patients who had progressed on one prior second-generation ARPI. The following patients were not allowed in the study; patients that had received cytotoxic chemotherapy (including, e.g., docetaxel), except in the (neo)adjuvant setting if this was at least 12 months ago; patients eligible for treatments other than ARPIs based on the presence of any mutations or biomarkers that are known as predictors of better response (e.g, AR-V7 or BRCA); patients previously progressed or having had intolerable toxicity to both enzalutamide and abiraterone. This generally corresponds to the proposed indication with a few exceptions; patients needed to be taxane-naïve; however, this is not reflected in the wording of the indication; and patients were included without eligibility criteria for symptoms. However, the currently proposed indication wording, i.e., “*who are asymptomatic or mildly symptomatic*” does not reflect the PSMAfore ITT study population but is based on a post-hoc defined patient subgroup. Importantly, this subgroup is not considered one “*where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed*” ([EMA/CHMP/539146/2013](#)). It, instead, merely seems an attempt to make the inferior comparator more acceptable (comparator to be discussed below in more detail), mirroring the wording used for the approved agents used as comparator in the study, i.e., [abiraterone](#) or [enzalutamide](#) which

both include the wording “*who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated*”. Importantly though, these approved indications concern an earlier mCRPC treatment line, i.e., following ADT only. Thus, the wording of the indication does not correspond to the PSMAfore eligibility criteria and is, therefore, no adequate reflection of the studied patient population (**part of MO**).

Further, patients were required to have a positive Gallium scan defined as a lesion showing a greater uptake intensity compared to background liver uptake (additional requirements were defined for patients with soft tissue disease). This is similar to the definition used in the pivotal study for the MAA (procedure EMEA/H/C/005483/0000; [EPAR](#)) and is reflected in the indication and, therefore, considered acceptable.

Study treatments

In the ¹⁷⁷Lu-PSMA-617 arm patients received a dose of 7.4 GBq (200 mCi) ± 10% of lutetium (¹⁷⁷Lu) vipivotide tetraxetan which was administered once every 6 weeks (1 cycle) for 6 cycles. This is in accordance with the approved posology and therefore acceptable. Treatment in the ARPI arm included abiraterone (±prednisone/ prednisolone) or enzalutamide as per approved local labels and guidelines. The [EAU](#) and [ESMO guidelines](#), however, state that sequencing of androgen receptor targeted agents should be avoided as there is evidence suggesting cross-resistance between abiraterone and enzalutamide. Moreover, a second AR inhibitor has shown only modest activity. Therefore, it is considered that the control arm treatment in this study is inadequate (**part of MO**). This is particularly of concern as therapies exist which have shown an OS benefit in this setting (e.g., taxane-based chemotherapy) which should have been the control arm in this study. The issue of an inadequate control arm was also highlighted in CHMP scientific advice in 2024 (which concerned a different medicinal product of the MAH).

The choice of control arm is also not supported by scientific literature ([van Wambeke et al. J Clin Oncol. 2022](#); [Rahbar and Boegemann. J Nucl Med. 2024](#); [Schnog et al. BJC Reports. 2024](#); [Mateo and Zurita. Lancet Oncol. 2024](#)). Moreover, the very recently reported results of the randomized phase II CCTG PR.21 study ([NCT04663997](#)) conducted in the same setting show that there was no indication of an rPFS benefit of ¹⁷⁷Lu-PSMA-617 versus docetaxel (median rPFS 8.6 vs 10.7 months, respectively), while there was a possible OS detriment (median OS 14.3 vs 18.2 months, respectively) ([Chi et al. ESMO 2025 abstract](#)).

Of note, all patients in the pivotal study PSMAfore were required to have a castrate level of serum/plasma testosterone and this should be reflected in the wording of the indication (**part of MO**).

Objectives/endpoints

The primary objective of the study was to evaluate rPFS assessed by BICR. This endpoint has been a primary endpoint in prostate cancer studies; however, OS has been considered the relevant endpoint for approval specifically as other treatments in this setting have shown survival advantage.

Furthermore, rPFS has not been established as surrogate endpoint for OS ([Gharzai et al. NEJM Evid. 2023](#)) in CRPC. Therefore, OS results are considered to be of utmost importance. OS is a key secondary endpoint, which is considered acceptable. However, the allowance of cross-over to ¹⁷⁷Lu-PSMA-617 which is not an approved/established treatment in taxane-naïve patients, will severely limit the ability to draw a conclusion on this endpoint and, therefore, this is considered an important limitation of the study design (**part of MO**). The other secondary and exploratory endpoints are considered acceptable. Progressive mCRPC was defined by the PCWG3 criteria, as is the assessment schedule which is in accordance with clinical guidelines and therefore acceptable.

The estimand for the primary objective is clearly defined and agreed. The primary clinical question of interest, the strategies for handling intercurrent events and the rPFS analysis are in line with the approach preferred by the CHMP.

Sample size

Overall, a total study sample size of approximately 450 participants were to be randomly assigned to each treatment arm in a 1:1 ratio. The sample size calculation was based on the primary variable rPFS powered at 95% and key secondary variable OS powered at 80%. The assumptions stated as part of the calculations, and magnitude of the treatment effects are agreed. For rPFS, 156 events were required to be observed and 297 deaths for OS. Although OS was powered at 80%, this did not take the potential impact of crossover into account and/or was based on a strong benefit in patients who were initially allocated to the treatment arm.

Statistical methods

The primary efficacy analysis to compare the two treatment groups on rPFS was in line with standard methods, i.e., stratified log-rank and stratified cox proportional hazards model.

Patients without radiographic progression or death were to be censored at the date of the last adequate assessment. For the primary analysis, patients with two or more missing assessments prior to an rPFS event were to be censored at the last adequate assessment, along with those who did not have any adequate post-baseline assessments. While the last two represent examples of non-administrative censoring, relevant sensitivity analyses that address the sensitivity of the results to these censoring rules have been pre-specified.

For the key secondary endpoint of OS, the plan for the main analysis was to follow the ITT principle based on the FAS population according to the treatment group and strata assigned at randomisation. The stratified log-rank test was to be used for inference, and the hazard ratio for OS was to be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. Three interim analyses plus the final OS analysis were planned.

Since participants in the ARPI arm were allowed to crossover to the ¹⁷⁷Lu-PSMA-617 arm upon confirmation of rPFS by BICR, adjustment for the effect of crossover on OS was pre-planned as a supplementary analyses. The RPSFT model was described as the intended method to adjust OS for crossover, although it was stated that other methods were also allowed. The results of OS analyses adjusted to cross-over are not considered reliable as it is not known whether the model assumptions are met.

Technical details of RPSFT, IPCW and the two-part method are available in version 5.0 of the SAP (release date 17-May-2024), however there are no details on the selection of any covariates that are required for these models. Further, the date of the SAP version 5.0 is after the results of the RPSFT model would have been known (the relevant table in the main CSR is dated 5-Apr-2024). In order to understand when and how IPCW was planned, all versions of the SAP are requested (**OC**).

Imaging data needed for the IPCW analysis were initially not collected, however at the request of the FDA on 07-Feb-2025 (thus after the final OS DCO of 01-Jan-2025) imaging data were retrospectively collected. Candidate co-variables were not prespecified in the protocol/SAP, however the MAH states that these were determined prior to database lock. This is not understood as the MAH has stated that the decision for IPCW was made after the final OS DCO. Moreover, multiple models were fitted and it is not clear how the final model was chosen. Thus, it appears that methods for IPCW models were made with knowledge of the data, i.e., data driven.

No formal statistical tests were performed for PRO data and no multiplicity adjustment was applied. Also no minimal important difference was defined. Therefore, PRO data are considered to be exploratory and not sufficiently reliable to report in the SmPC.

Conduct of the study

The protocol was amended 3 times. A third OS interim analysis was added after the DCO of the primary PFS analysis and first OS interim analyses, thus with knowledge of outcomes, however considering that the final OS analysis is not statistically significant, this issue is not pursued. The protocol amendments are not considered to have had a large influence on the interpretation and reliability of the data.

Though there were many protocol deviations, the deviations were generally balanced between treatment arms. A considerable part of the protocol deviations were related to a 3-week production halt of AAA617, and due to incorrectly collected blood biomarker samples and ePRO at timepoints which were not specified for this study during the production halt. The deviations are considered not to have a large impact on the data quality. However there were patients with a deviation of eligibility criteria, which may be protocol violations. The MAH should clarify why inclusion of these patients does not lead to issues with data quality (OC).

Efficacy data and additional analyses

Analyses and DCOs

Multiple DCOs are used in this application. Results are based on the primary analysis rPFS by BIRC using a DCO of 02-Oct-2022 and the final analysis of OS using a DCO of 01-Jan-2025. Demographics, secondary and exploratory efficacy data, including updated data for rPFS, are presented using a DCO of 27-Feb-2024 (corresponding to the 3rd OS IA). Post-hoc analyses of efficacy endpoints have also been submitted.

At the DCO date of 01-Jan-2025, the final OS analysis included 468 randomized participants (n=234 in ¹⁷⁷Lu-PSMA-617 arm, n=234 in ARPI arm). The median duration of study (from randomization to data cut-off) was 34.3 months (range: 26.9 - 42.1) vs 34.3 months (range: 27.7 - 42.2), respectively. At the time of the 3rd OS IA (DCO of 27-Feb-2024) the same number of patients were included as in the final analysis. The median duration of study was 24.1 months (range: 16.7 - 32.0) vs. 24.1 months (range: 17.5 - 32.0) respectively. At the time of the primary rPFS analysis (DCO of 02-Oct-2022), a total of 467 participants (n=233 in ¹⁷⁷Lu-PSMA-617 arm, n=234 in ARPI arm) were included. The median duration of study was 7.26 months (range: 0.8 - 15.1) vs. 7.28 months (range: 0.7 - 15.1), respectively.

Baseline data

At the DCO of 27-Feb-2024 (3rd OS IA), baseline patient and disease characteristics were generally balanced between the two study arms and representative of the target population. There was a concordance of 77% between IRT and source data for the randomization factors (see also below). According to source data 50.9% were asymptomatic/mildly symptomatic, 38% symptomatic 11.1% missing in the ¹⁷⁷Lu-PSMA-617 arm versus 57.7%, 33.3% and 9% in the ARPI arm. Based on these characteristics it becomes clear that patients "*who are asymptomatic or mildly symptomatic*" is a post-hoc subgroup selection and 49% of the study patients fall outside this definition. Of note, as over half of patients received chemotherapy as subsequent anti-cancer therapy, it could be questioned whether the PSMAfore patient population truly consisted of patients for whom chemotherapy was not (yet) clinically indicated (in line with the proposed indication).

Outcomes

At the DCO of 02-Oct-2022, the primary endpoint rPFS demonstrated a statistically significant improvement of ¹⁷⁷Lu-PSMA-617 over ARPI (HR = 0.41; 95% CI: 0.29, 0.56; p<0.0001) in the ITT/FAS. The median follow-up time for rPFS was 4.09 months in ¹⁷⁷Lu-PSMA-617 arm versus 2.37 months in ARPI arm. The estimated median rPFS was 9.30 months (95% CI: 6.77, NE) vs. 5.55

months (95% CI: 4.04, 5.95), respectively. The KM curves separate after two months and remain separated thereafter, although there is a lot of censoring throughout the KM curves. rPFS was generally robust in sensitivity analyses and consistent in subgroup analyses. There was a rPFS discordance rate of 10.3% in the ¹⁷⁷Lu-PSMA-617 arm and 17.9% in the ARPI arm between the BICR and the investigator. The discordance was due to the BICR assigning PD more often and the investigator censoring more often in both treatment arms. As the investigator PFS HR was 0.46 (95%CI: 0.32, 0.65), the discordance has not had a great impact on the results. An updated analysis of rPFS was conducted at the 27-Feb-2024 DCO. The results of this exploratory analysis are in line with the results from the primary analysis (HR 0.49; median rPFS 11.6 vs 5.6 months, respectively). The KM curves continue to show clear separation with less censoring, but approach each other after 26 months.

Thus, ¹⁷⁷Lu-PSMA-617 treatment results in a delay of radiographic progression compared to an inadequate/ineffective control treatment.

The key secondary endpoint OS was not met in this study. The final OS analysis (DCO: 01-Jan-2025) was based on 299 deaths (~100% information fraction; 60.7% event in the ¹⁷⁷Lu-PSMA-617 arm and 67.1% in the ARPI arm), thus the OS data is considered to be mature. The HR (95% CI) for OS was 0.91 (0.72, 1.14) and one-sided p-value was 0.20. The median OS (95% CI) was 24.5 months (19.6, 28.9) and 23.1 months (19.6, 25.5), respectively. The KM-curves for OS do not separate. Concluding, ¹⁷⁷Lu-PSMA-617 treatment in this setting does not result in an OS benefit.

There is no consistent support from other secondary endpoints (DCO 27-Feb-2024). PFS and TT (time to) symptomatic skeletal events (SSE) and soft tissue progression (STP) support rPFS in other words progression appears to be delayed with ¹⁷⁷Lu-PSMA-617 treatment. However, progression/death on next therapy or time to chemotherapy are not delayed compared to the control group, again questioning the clinical relevance of the delay in progression.

Time to worsening of HRQoL is generally shorter in the ARPI arm vs the ¹⁷⁷Lu-PSMA-617 arm, however methodological issues limit the interpretability of HRQoL.

Exploratory/ancillary analyses

Exploratory endpoint ORR (DCO 27-Feb-2024) indicates a large difference in rates between the ¹⁷⁷Lu-PSMA-617 arm (48.6%) vs the ARPI arm (13.9%), however it also points out that responses in the ARPI arm are generally poor and, therefore, that ARPI switch is an inadequate control treatment with low antitumour activity.

At the time of the DCO for the final OS analysis (DCO 01-JAN-2025) 141/234 (60.3%) of the patients in the ARPI arm had crossed over to receive ¹⁷⁷Lu-PSMA-617. Multiple analyses to adjust OS for crossover were performed. In the RPSFT method (intended method for crossover adjustment) a HR of 0.84 (95% CI: 0.55, 1.28) was observed. Thus, not indicating an OS benefit. OS in the IPCW analysis resulted in a HR of 0.59 (95% CI: 0.38, 0.91) with different IPCW models showing HRs ranging from 0.54 to 0.62. As stated in the section on study design, the results of OS analyses adjusted to crossover are not reliable as it is not known whether the model assumptions are met and due to the possible data-driven methods to not only choose to perform the IPCW analysis, but also the selection of the covariates that are required to include in this analysis. Additionally, the two-stage method that was also described in SAP version 5.0 was not reported at all.

Post-hoc OS analyses which were stratified by source data rather than data in the IRT indicated that a rPFS HR of 0.35 [95%CI: 0.22, 0.56] and an OS HR 0.72 [95%CI: 0.52, 1.00]. In these analyses still no OS benefit is shown and the post-hoc nature of these analyses limits their reliability.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

5.4. Conclusions on the clinical efficacy

Treatment with ¹⁷⁷Lu-PSMA-617 showed an improvement in rPFS only compared to a switch in ARPI in mCRPC patients who have progressed on one prior second-generation ARPI. However, ARPI switch is considered an inadequate and ineffective control treatment, as such the clinical relevance of the rPFS effect is unclear. The final and mature OS analysis failed to reach statistical significance. Some secondary endpoints (TTSSE, TTSTP, PFS) support the primary endpoint, while others are in line with the lack of OS benefit (PFS2, TTCT). OS has been considered the relevant endpoint for approval specifically as other treatments in this setting have shown a survival advantage. Furthermore, rPFS has not been established as surrogate endpoint for OS in CRPC. Therefore, the lack of OS benefit is considered to be an important shortcoming.

Crossover to ¹⁷⁷Lu-PSMA-617 was allowed in the study design, which is considered to be a great drawback in the design as ¹⁷⁷Lu-PSMA-617 is not an approved treatment option in taxane-naïve patients. OS analyses adjusting for crossover demonstrate inconsistent results and are not considered to be reliable due to a possible data driven methodology and uncertainty whether model assumptions are met. Overall, benefit for ¹⁷⁷Lu-PSMA-617 treatment has not been established (**MO**).

In addition, the wording of the indication is not agreed and should be amended (**MO**)

6. Clinical safety

6.1. Introduction

Safety evaluation for the newly applied indication “*treatment of patients with prostate- specific membrane antigen (PSMA) positive metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) therapy and for whom chemotherapy is not yet clinically indicated* for Pluvicto (¹⁷⁷Lu vipivotide tetraxetan) is based on safety data set from the pivotal Study B12302 using the final OS analysis DCO date of 01-Jan-2025 and data from Study PSMA-617-01 (VISION) using the DCO date of 14-Dec-2023.

The following analysis sets were utilized for evaluation of safety in this study:

The **Safety Set B** included all patients who received at least one dose of study treatment (i.e. at least one dose of (AAA617 or ARPI/ARDTs) during the randomised part of the protocol. Patients were analyzed according to the study treatment received, where treatment received was defined as the randomised treatment if the patient took at least one dose of that treatment.

The **Lu-PSMA-617 Safety Set** included all patients who received at least one dose of AAA617 during the randomised part of the protocol or after crossover.

The terms ARPI/ARDT and androgen receptor-directed therapy (ARDT) are used interchangeably in this document.

In addition, post-marketing data from the most recent PSUR (reporting period 23-Sep-2024 to 22-Mar-2025) are provided.

Safety topics of interest (STIs) for A177Lu vipivotide tetraxetan were identified based on the mechanism of action of AAA617, biological plausibility, clinical observations from the initial VISION trial PSMA-617-01 from which meanwhile long term data is available.

STIs included the following:

- Myelosuppression
- Renal toxicity
- Dry mouth
- Dry eye
- Fractures
- Intracranial haemorrhage
- Second primary malignancies
- QT prolongation
- Hepatotoxicity
- Radiotoxicity including inadvertent exposure

6.2. Patient exposure

Overall, for the pooled safety dataset, 927 patients received at least one dose of AAA617 for a median of 8.3 months and a total of 648.5 patient-years (Table 1-4).

Among patients who received AAA617 in the pooled safety dataset, the median number of doses of AAA617 received was 6.0 (range: 1-6).

In the ARDT arm of Study B12302, 232 patients received at least one dose of oral ARPI/ARDT (either abiraterone or enzalutamide). The median duration of exposure in this arm was 6.5 months (range: 0.03-39.39) (Table 1-4).

Both the cumulative dose of AAA617 received and dose intensity are provided in Table 1-5.

Among patients who received AAA617 in the pooled safety dataset, the median (min-max) cumulative AAA617 dose received was 39.0 (6.9-48.3) GBq. The median (min-max) dose intensity was 5.28 (3.1-25.3) GBq/month. The median (min-max) relative dose intensity was 100.27% (76.0-471.3) with the majority of patients (95.3%) in the relative dose intensity category of >90-110%.

Of note, the maximum dose intensity of 25.3 GBq/month and maximum relative dose intensity of 471.3% is related to a patient in Study PSMA-617-01 who received only 1 dose at Cycle 1 but withdrew consent 8 days later to pursue off-study treatment. Two other patients in Study PSMA-617-01 had maximum relative dose >200%. They received only 1 dose at Cycle 1 but then died within 1 month of their dose. All 3 patients had received the dose as planned per protocol [Study PSMA-617-01 Primary Analysis-Section 10.5.1.2.2].

In the ARPI/ARDT arm of Study B12302, patients reported a median relative dose intensity of ARPI/ARDT of 100.00% (range: 50.8-100.00) (Table 1-5).

Table 1-4 Duration of exposure to study treatment (Safety set)

	PSMAfore Randomised [177Lu] Lu-PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [177Lu]Lu- PSMA-617 N=141	VISION [177Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [177Lu]Lu- PSMA-617 Patients N=927
Duration of exposure (months)					
Mean (SD)	7.433 (2.4830)	9.001 (8.2288)	6.310 (2.6250)	9.311 (6.6815)	8.395 (5.5536)
Median	8.411	6.538	7.162	7.819	8.279
Min-Max	0.36-11.63	0.03-39.39	0.49-11.04	0.33-36.50	0.33-36.50
Duration of exposure categories-n (%)					
Less than 1 month	1 (0.4)	5 (2.2)	2 (1.4)	3 (0.5)	6 (0.6)
At least 1 month	226 (99.6)	227 (97.8)	139 (98.6)	556 (99.5)	921 (99.4)
At least 6 months	171 (75.3)	128 (55.2)	80 (56.7)	336 (60.1)	587 (63.3)
At least 12 months	0	49 (21.1)	0	138 (24.7)	138 (14.9)
At least 18 months	0	29 (12.5)	0	61 (10.9)	61 (6.6)
At least 24 months	0	17 (7.3)	0	27 (4.8)	27 (2.9)
At least 39 months	0	1 (0.4)	0	0	0
Number of AAA617 doses					
Mean (SD)	5.0 (1.55)	-	4.4 (1.78)	4.4 (1.69)	4.6 (1.69)

	PSMAfore	PSMAfore	PSMAfore	VISION	All mCRPC
	Randomised [¹⁷⁷ Lu] Lu-PSMA-617 N=227	Randomised ARDT N=232	Crossover [¹⁷⁷ Lu]Lu- PSMA-617 N=141	[¹⁷⁷ Lu]Lu- PSMA-617 +BSC/BSoc N=559	[¹⁷⁷ Lu]Lu- PSMA-617 Patients N=927
Median	6.0	-	5.0	5.0	6.0
Min-Max	1-6	-	1-6	1-6	1-6
Number of AAA617 doses (categori es)-n (%)					
At least 1 injection	227 (100)		141 (100)	559 (100)	927 (100)
At least 2 injections	220 (96.9)		132 (93.6)	525 (93.9)	877 (94.6)
At least 3 injections	197 (86.8)		111 (78.7)	463 (82.8)	771 (83.2)
At least 4 injections	180 (79.3)		90 (63.8)	378 (67.6)	648 (69.9)
At least 5 injections	165 (72.7)		79 (56.0)	302 (54.0)	546 (58.9)
6 injections	144 (63.4)		68 (48.2)	256 (45.8)	468 (50.5)
Patient-time (years)	140.6	174.0	74.1	433.8	648.5

Patient-time is the sum of each patient's treatment exposure in years.

In Study PSMA-617-01, patients were allowed to continue BSC/BSoc alone after discontinuation or completion of [¹⁷⁷Lu]Lu-PSMA-617, which extends the exposure beyond the maximum of 6 cycles in the [¹⁷⁷Lu]Lu-PSMA-617+BSC/BSoc arm.

Source: [SCS Appendix 1-Table 1-1]

Table 1-5 Dose of study treatment received (Safety set)

	PSMAfore Randomised [¹⁷⁷ Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [¹⁷⁷ Lu]Lu- PSMA-617 N=141	VISION [¹⁷⁷ Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [¹⁷⁷ Lu]Lu- PSMA-617 Patients N=927
Cumulative dose (GBq)					
Mean (SD)	35.93 (11.205)	31.56 (12.800)		33.16 (12.739)	33.60 (12.462)
Median	42.39	36.47		37.36	39.00
Min-Max	7.0-45.4	6.9-46.0		7.0-48.3	6.9-48.3
Dose intensity (GBq/month)					
Mean (SD)	4.97 (1.079)		5.14 (1.022)	5.46 (1.208)	5.29 (1.170)
Median	4.95		5.11	5.44	5.28
Min-Max	3.7-20.0		3.4-14.9	3.1-25.3	3.1-25.3
Relative dose intensity (%)					
Mean (SD)	4.97 (1.079)	95.96 (9.499)	96.70 (4.555)	104.26(21.395)	101.32 (17.201)
Median	4.95	100.00	97.57	102.50	100.27
Min-Max	3.7-20.0	50.8-100.0	76.0-106.7	90.5-471.3	76.0- 471.3
Relative dose intensity categories -n (%)					
<=75%	0	13 (5.6)	0	0	0
>75-90%	12 (5.3)	21 (9.1)	10 (7.1)	0	22 (2.4)
>90-110%	215 (94.7)	198 (85.3)	131 (92.9)	537 (96.1)	883 (95.3)

	PSMAfore Randomised [¹⁷⁷Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [¹⁷⁷Lu]Lu- PSMA-617 N=141	VISION [¹⁷⁷Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [¹⁷⁷Lu]Lu- PSMA-617 Patients N=927
>110%	0	0	0	22 (3.9)	22 (2.4)

Dose intensity and relative dose intensity include days of zero dose in the calculation.

Dose intensity is defined as cumulative dose of study treatment divided by duration of exposure to study treatment (AAA617, or ARDT in PSMAfore randomised ARDT arm). Relative dose intensity is defined as dose intensity divided by planned dose intensity. Conversion factor for [¹⁷⁷Lu]Lu-PSMA-617 - 1 mCi = 0.037 GBq; 1 MBq = 0.001 GBq. Source: [SCS Appendix 1-Table 1-2]

Table 1-6 Disposition (Safety set)

Disposition Reason	PSMAfore Randomised [¹⁷⁷Lu]Lu- PSMA- 617 N=227	PSMAfore Randomised ARDT N=232	VISION [¹⁷⁷Lu]Lu- -PSMA- 617 +BSC/BSoc N=559	All mCRPC Randomised [¹⁷⁷Lu]Lu- PSMA-617 Patients N=786
	n (%)	n (%)	n (%)	n (%)
	n (%)	n (%)	n (%)	n (%)
Patients randomised	227 (100)	232 (100)	559 (100)	786 (100)
Treated	227 (100)	232 (100)	559 (100)	786 (100)
Treatment ongoing *	0	9 (3.9)	0	0
Completed treatment	131 (57.7)	0	260 (46.5)	391 (49.7)
Discontinued from treatment	96 (42.3)	223 (96.1)	299 (53.5)	395 (50.3)
Reason for discontinuation				
Progressive disease	54 (23.8)	173 (74.6)	134 (24.0)	188 (23.9)
Physician decision	24 (10.6)	32 (13.8)	20 (3.6)	44 (5.6)
Adverse event	12 (5.3)	12 (5.2)	57 (10.2)	69 (8.8)
Patient decision	5	(2.2)	5	(2.2)
Lost to follow-up	1	(0.4)		0
Death		0	1	(0.4)
No longer clinically benefiting		0		0
Other		0		0
Patient requires care not allowed in the study		0		0
Withdrew consent		0		0

*Ongoing at the time of the data cut-off date . Treatment ongoing and completed treatment are based on AAA617 or ARDT.

Source: [SCS Appendix 1-Table 2-1]

Table 1-7 Disposition for crossover patients in Study B12302 (Safety set)

Disposition Reason	PSMAfore Randomised ARDT N=232 n (%)
Entered crossover treatment period	141 (60.8)
Treatment ongoing *	3 (1.3)

Completed treatment	61 (26.3)
Discontinued from treatment	77 (33.2)
Reason for discontinuation	
Progressive disease	45 (19.4)
Physician decision	16 (6.9)
Adverse event	8 (3.4)
Patient decision	5 (2.2)
Death	3 (1.3)

*Ongoing at the time of the data cut-off date.

Treatment ongoing and Completed treatment are based on AAA617 or ARDT. Source: [SCS Appendix 1-Table 2-1]

6.3. Adverse events

6.3.1. Analysis of adverse events

In Study B12302, the proportion of SAEs was lower in the AAA617 arm compared to the ARPI/ARDT arm; however, treatment-related SAEs were comparable. The overall incidences of TEAEs for Study B12302 and Study PSMA-617-01 are shown in Table 2-1:

Table 2-1 Overview of adverse events (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
Category	All grades N(%)	Grade ≥3	All grades N(%)	Grade ≥3	All grades N(%)	Grade ≥3	All grades N(%)	Grade ≥3	All grades N(%)	Grade ≥3
Adverse events	224 (98.7)	80 (35.2)	228 (98.3)	11 (49.1)	136 (96.5)	55(39.0)	548 (98.0)	295 (52.8)	908 (98.0)	430 (46.4)
Treatment related	203 (89.4)	31 (13.7)	148 (63.8)	28 (12.1)	120 (85.1)	19 (13.5)	470 (84.1)	158 (28.3)	793 (85.5)	208 (22.4)
Serious Adverse Events	46 (20.3)	41 (18.1)	76 (32.8)	70 (30.2)	40 (28.4)	34 (24.1)	204 (36.5)	181 (32.4)	290 (31.3)	256 (27.6)
Treatment-related	9 (4.0)	8 (3.5)	6 (2.6)	6 (2.6)	5 (1.4)	53 (9.5)	48 (8.6)	67 (7.2)	58 (6.3)	58 (6.3)
Fatal serious adverse events	4 (1.8)	4 (1.8)	5 (2.2)	5 (2.2)	3 (2.1)	21 (3.8)	21 (3.8)	28 (3.0)	28 (3.0)	28 (3.0)
Treatment-related	0	0	1 (0.4)	1 (0.4)	0	0	5 (0.9)	5 (0.9)	5 (0.5)	5 (0.5)
Adverse events leading to discontinuation*	12 (5.3)	7 (3.1)	12 (5.2)	9 (3.9)	8 (5.7)	4 (2.8)	65 (11.6)	39 (7.0)	85 (9.2)	50 (5.4)
Treatment-related	9 (4.0)	4 (1.8)	6 (2.6)	3 (1.3)	4 (2.8)	0	42 (7.5)	26 (4.7)	55 (5.9)	30 (3.2)
Adverse events leading to dose adjustment*	8 (3.5)	3 (1.3)	36 (15.5)	7 (3.0)	10 (7.1)	3 (2.1)	32 (5.7)	12 (2.1)	50 (5.4)	18 (1.9)
Adverse events leading to dose interruption*	29 (12.8)	13 (5.7)	45 (19.4)	20 (8.6)	16 (11.3)	9 (6.4)	89 (15.9)	46 (8.2)	134 (14.5)	68 (7.3)

Numbers (n) represent counts of patients.

*of AAA617 or ARDT for PSMAfore and AAA617 for VISION.

Summary of adverse events that occurred: PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or

last dose date of [177Lu]Lu-PSMA-617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first. Adverse event relationship to study drug in VISION study could not make the distinction whether the AE was related to AAA617 or BSC/BSoC. MedDRA version 27.1, CTCAE version V5.0.

Source: [SCS Appendix 1-Table 5-1]

6.3.2. Adverse events by system organ class

The incidence of TEAEs by primary SOC is shown in Table 2-2.

Table 2-2 TEAEs by primary system organ class (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	224 (98.7)	80 (35.2)	228(98.3)	114 (49.1)	136 (96.5)	55 (39.0)	548 (98.0)	295 (52.8)	908 (98.0)	430 (46.4)
Blood and lymphatic system disorders	79 (34.8)	24 (10.6)	53 (22.8)	20 (8.6)	52 (36.9)	11 (7.8)	265 (47.4)	133 (23.8)	396 (42.7)	168 (18.1)
Cardiac disorders	14 (6.2)	6 (2.6)	15 (6.5)	3 (1.3)	9 (6.4)	4 (2.8)	25 (4.5)	11 (2.0)	48 (5.2)	21 (2.3)
Congenital, familial and genetic disorders	0	0	2 (0.9)	0	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Ear and labyrinth disorders	9 (4.0)	0	8 (3.4)	0	2 (1.4)	0	17 (3.0)	0	28 (3.0)	0
Endocrine disorders	2 (0.9)	1 (0.4)	3 (1.3)	0	1 (0.7)	0	10 (1.8)	1 (0.2)	13 (1.4)	2 (0.2)
Eye disorders	20 (8.8)	0	13 (5.6)	2 (0.9)	9 (6.4)	0	53 (9.5)	6 (1.1)	82 (8.8)	6 (0.6)
Gastrointestinal disorders	191 (84.1)	8 (3.5)	99 (42.7)	5 (2.2)	103 (73.0)	8 (5.7)	420 (75.1)	33 (5.9)	714 (77.0)	49 (5.3)
General disorders and administration site conditions	146 (64.3)	8 (3.5)	153 (65.9)	22 (9.5)	69 (48.9)	8 (5.7)	337 (60.3)	52 (9.3)	552 (59.5)	68 (7.3)
Hepatobiliary disorders	4 (1.8)	0	7 (3.0)	4 (1.7)	1 (0.7)	0	13 (2.3)	5 (0.9)	18 (1.9)	5 (0.5)
Immune system disorders	2 (0.9)	0	4 (1.7)	1 (0.4)	0	0	1 (0.2)	0	3 (0.3)	0
Infections and infestations	78 (34.4)	13 (5.7)	72 (31.0)	19 (8.2)	29 (20.6)	9 (6.4)	176 (31.5)	59 (10.6)	283 (30.5)	81 (8.7)
Injury, poisoning and procedural complications	26 (11.5)	4 (1.8)	34 (14.7)	12 (5.2)	20 (14.2)	3 (2.1)	104 (18.6)	18 (3.2)	150 (16.2)	25 (2.7)
Investigations	76 (33.5)	27 (11.9)	75 (32.3)	17 (7.3)	42 (29.8)	14 (9.9)	137 (24.5)	16 (2.9)	255 (27.5)	57 (6.1)
Metabolism and nutrition disorders	67 (29.5)	3 (1.3)	76 (32.8)	13 (5.6)	47 (33.3)	4 (2.8)	229 (41.0)	34 (6.1)	343 (37.0)	41 (4.4)
Musculoskeletal and connective tissue disorders	113 (49.8)	9 (4.0)	146 (62.9)	19 (8.2)	70 (49.6)	4 (2.8)	327 (58.5)	53 (9.5)	510 (55.0)	66 (7.1)
Neoplasms benign malignant	6 (2.6)	3 (1.3)	8 (3.4)	3 (1.3)	3 (2.1)	0	19 (3.4)	7 (1.3)	28 (3.0)	10 (1.1)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Nervous system disorders	69 (30.4)	3 (1.3)	81 (34.9)	16 (6.9)	37 (26.2)	4 (2.8)	190 (34.0)	39 (7.0)	296 (31.9)	46 (5.0)
Product issues	1 (0.4)	0	1 (0.4)	0	0	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Psychiatric disorders	17 (7.5)	1 (0.4)	35 (15.1)	0	10 (7.1)	0	75 (13.4)	8 (1.4)	102 (11.0)	9 (1.0)
Renal and urinary disorders	29 (12.8)	5 (2.2)	56 (24.1)	16 (6.9)	24 (17.0)	3	(2.1)	111 (19.9)	39 (7.0)	164 (17.7)
Reproductive system and breast disorders	7 (3.1)	0	10 (4.3)	0	3 (2.1)		0	17 (3.0)	2 (0.4)	27 (2.9)
Respiratory, thoracic and mediastinal disorders	43 (18.9)	3 (1.3)	43 (18.5)	11 (4.7)	22 (15.6)	4	(2.8)	150 (26.8)	25 (4.5)	215 (23.2)
Skin and subcutaneous tissue disorders	25 (11.0)	0	23 (9.9)	0	15 (10.6)		0	74 (13.2)	0	114 (12.3)
Surgical and medical procedures	0	0	0	0	0		0	5 (0.9)	3 (0.5)	5 (0.5)

Numbers (n) represent counts of patients.

A patient with multiple severity grades for an adverse event is only counted under the maximum grade.

Primary system organ classes are sorted in alphabetical order.

Summary of adverse events that occurred:

PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first.

MedDRA version 27.1, CTCAE version V5.0.

Source: [SCS Appendix 1-Table 5-7]

Adverse events by preferred term

The most frequent TEAEs (in at least 5% of patients in any treatment arm), irrespective of causality, are shown in [Table 2-3](#). **Table 2-3 TEAEs in at least 5% of patients in any treatment group – by preferred term (Safety set)**

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	224 (98.7)	80 (35.2)	228 (98.3)	114 (49.1)	136 (96.5)	55 (39.0)	548 (98.0)	295 (52.8)	908 (98.0)	430 (46.4)
Dry mouth	135 (59.5)	2 (0.9)	6 (2.6)	0	73 (51.8)	0	210 (37.6)	0	418 (45.1)	2 (0.2)
Nausea	74 (32.6)	0	29 (12.5)	1 (0.4)	42 (29.8)	0	200 (35.8)	7 (1.3)	316 (34.1)	7 (0.8)
Fatigue	54 (23.8)	1 (0.4)	59 (25.4)	4 (1.7)	18 (12.8)	2 (1.4)	234 (41.9)	32 (5.7)	306 (33.0)	35 (3.8)
Anaemia	62 (27.3)	14 (6.2)	45 (19.4)	16 (6.9)	39 (27.7)	7 (5.0)	179 (32.0)	72 (12.9)	280 (30.2)	93 (10.0)
Decreased appetite	49 (21.6)	0	44 (19.0)	2 (0.9)	28 (19.9)	0	115 (20.6)	10 (1.8)	192 (20.7)	10 (1.1)
Arthralgia	46 (20.3)	0	54 (23.3)	1 (0.4)	19 (13.5)	0	121 (21.6)	6 (1.1)	186 (20.1)	6 (0.6)
Constipation	50 (22.0)	1 (0.4)	33 (14.2)	0	22 (15.6)	1 (0.7)	110 (19.7)	6 (1.1)	182 (19.6)	8 (0.9)
Back pain	31 (13.7)	3 (1.3)	46 (19.8)	6 (2.6)	18 (12.8)	1 (0.7)	130 (23.3)	19 (3.4)	179 (19.3)	23 (2.5)
Diarrhoea	38 (16.7)	0	23 (9.9)	1 (0.4)	15 (10.6)	0	104 (18.6)	4 (0.7)	157 (16.9)	4 (0.4)
Vomiting	26 (11.5)	0	12 (5.2)	0	26 (18.4)	2 (1.4)	104 (18.6)	5 (0.9)	156 (16.8)	7 (0.8)
Asthenia	73 (32.2)	2 (0.9)	67 (28.9)	8 (3.4)	30 (21.3)	2 (1.4)	35 (6.3)	7 (1.3)	138 (14.9)	11 (1.2)
Thrombocytopenia	18 (7.9)	5 (2.2)	7 (3.0)	2 (0.9)	17 (12.1)	1 (0.7)	95 (17.0)	44 (7.9)	130 (14.0)	50 (5.4)
Bone pain	20 (8.8)	1 (0.4)	18 (7.8)	2 (0.9)	14 (9.9)	2 (1.4)	61 (10.9)	15 (2.7)	95 (10.2)	18 (1.9)
Lymphopenia	4 (1.8)	1 (0.4)	0	0	3 (2.1)	1 (0.7)	80 (14.3)	42 (7.5)	87 (9.4)	44 (4.7)
Oedema peripheral	19 (8.4)	0	29 (12.5)	0	11 (7.8)	0	55 (9.8)	2 (0.4)	85 (9.2)	2 (0.2)
Weight decreased	15 (6.6)	1 (0.4)	32 (13.8)	4 (1.7)	10 (7.1)	2 (1.4)	59 (10.6)	2 (0.4)	84 (9.1)	5 (0.5)
Leukopenia	5 (2.2)	2 (0.9)	0	0	4 (2.8)	1 (0.7)	69 (12.3)	15 (2.7)	78 (8.4)	18 (1.9)
Urinary tract infection	12 (5.3)	3 (1.3)	12 (5.2)	5 (2.2)	3 (2.1)	2 (1.4)	61 (10.9)	21 (3.8)	76 (8.2)	26 (2.8)
Dyspnoea	11 (4.8)	1 (0.4)	14 (6.0)	6 (2.6)	6 (4.3)	1 (0.7)	57 (10.2)	8 (1.4)	74 (8.0)	10 (1.1)
Pain in extremity	17 (7.5)	1 (0.4)	27 (11.6)	1 (0.4)	9 (6.4)	0	47 (8.4)	4 (0.7)	73 (7.9)	5 (0.5)
Dizziness	11 (4.8)	0	13 (5.6)	0	8 (5.7)	0	45 (8.1)	5 (0.9)	64 (6.9)	5 (0.5)
Neutropenia	13 (5.7)	3 (1.3)	2 (0.9)	1 (0.4)	6 (4.3)	2 (1.4)	45 (8.1)	18 (3.2)	64 (6.9)	23 (2.5)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cough	15 (6.6)	0	12 (5.2)	0	5 (3.5)	0	42 (7.5)	0	62 (6.7)	0
Headache	19 (8.4)	0	11 (4.7)	0	2 (1.4)	0	39 (7.0)	4 (0.7)	60 (6.5)	4 (0.4)
Haematuria	4 (1.8)	0	18 (7.8)	3 (1.3)	7 (5.0)	1 (0.7)	47 (8.4)	13 (2.3)	58 (6.3)	14 (1.5)
Abdominal pain	12 (5.3)	2 (0.9)	11 (4.7)	1 (0.4)	9 (6.4)	0	33 (5.9)	5 (0.9)	54 (5.8)	7 (0.8)
Fall	6 (2.6)	0	14 (6.0)	1 (0.4)	6 (4.3)	0	39 (7.0)	1 (0.2)	51 (5.5)	1 (0.1)
Pyrexia	6 (2.6)	1 (0.4)	10 (4.3)	0	5 (3.5)	1 (0.7)	39 (7.0)	2 (0.4)	50 (5.4)	4 (0.4)
Blood creatinine increased	10 (4.4)	0	7 (3.0)	0	5 (3.5)	1 (0.7)	33 (5.9)	1 (0.2)	48 (5.2)	2 (0.2)
Dysgeusia	19 (8.4)	0	6 (2.6)	0	5 (3.5)	0	24 (4.3)	0	48 (5.2)	0
Hypocalcaemia	5 (2.2)	0	4 (1.7)	1 (0.4)	6 (4.3)	0	37 (6.6)	4 (0.7)	48 (5.2)	4 (0.4)
Hypokalaemia	5 (2.2)	2 (0.9)	19 (8.2)	4 (1.7)	3 (2.1)	0	40 (7.2)	5 (0.9)	48 (5.2)	7 (0.8)
Pain	7 (3.1)	1 (0.4)	16 (6.9)	5 (2.2)	4 (2.8)	0	35 (6.3)	8 (1.4)	46 (5.0)	9 (1.0)
Blood ALP Increased	14 (6.2)	7 (3.1)	18 (7.8)	6 (2.6)	9 (6.4)	4 (2.8)	22 (3.9)	6 (1.1)	45 (4.9)	17 (1.8)
COVID-19	37 (16.3)	1 (0.4)	29 (12.5)	1 (0.4)	5 (3.5)	0	3 (0.5)	1 (0.2)	45 (4.9)	2 (0.2)
Insomnia	8 (3.5)	0	13 (5.6)	0	3 (2.1)	0	30 (5.4)	0	41 (4.4)	0
Hypertension	7 (3.1)	3 (1.3)	23 (9.9)	7 (3.0)	3 (2.1)	1 (0.7)	30 (5.4)	16 (2.9)	40 (4.3)	20 (2.2)
Hot flush	15 (6.6)	0	22 (9.5)	0	2 (1.4)	0	22 (3.9)	0	39 (4.2)	0
Dry eye	14 (6.2)	0	2 (0.9)	0	6 (4.3)	0	16 (2.9)	0	36 (3.9)	0
Myalgia	13 (5.7)	0	13 (5.6)	1 (0.4)	5 (3.5)	0	18 (3.2)	0	36 (3.9)	0
Hypophosphataemia	2 (0.9)	0	7 (3.0)	0 4	(2.8)	2 (1.4)	28 (5.0)	5(0.9)	34 (3.7)	7 (0.8)
Musculoskeletal chest pain	10 (4.4)	0	16 (6.9)	0 4	(2.8)	0	17 (3.0)	0	31 (3.3)	0

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSOC N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lymphocyte count decreased	12 (5.3)	9 (4.0)	3 (1.3)	1 (0.4)	5 (3.5)	4 (2.8)	0	0	17 (1.8)	13 (1.4)
Platelet count decreased	6 (2.6)	2 (0.9)	2 (0.9)	0	7 (5.0)	1 (0.7)	0	0	13 (1.4)	3 (0.3)

Numbers (n) represent counts of patients.

Preferred terms are sorted by descending frequency in All mCRPC [177Lu]Lu-PSMA-617 Subjects 'All grades' column.

Summary of adverse events that occurred: PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first. MedDRA version 27.1, CTCAE version V5.0. Source: [SCS Appendix 1-Table 5-2]

6.3.3. Potential relationship of adverse events to study treatment

The treatment-related TEAEs that occurred in at least 5% of patients in any treatment arm are shown in [Table 2-5](#).

Table 2-4 Treatment-related TEAEs in at least 5% of patients in any treatment group – by preferred term (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoC N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	203(89.4)	31(13.7)	148(63.8)	28(12.1)	120(85.1)	19(13.5)	470(84.1)	158(28.3)	793(85.5)	208(22.4)
Dry mouth	131 (57.7)	2 (0.9)	2 (0.9)	0	69 (48.9)	0	194(34.7)	0	394(42.5)	2 (0.2)
Nausea	60 (26.4)	0	9 (3.9)	0	31 (22.0)	0	155(27.7)	5 (0.9)	246(26.5)	5 (0.5)
Fatigue	42 (18.5)	1 (0.4)	43 (18.5)	3 (1.3)	14 (9.9)	1 (0.7)	169(30.2)	22 (3.9)	225(24.3)	24 (2.6)
Anaemia	35 (15.4)	8 (3.5)	8 (3.4)	3 (1.3)	27 (19.1)	5 (3.5)	144(25.8)	53 (9.5)	206(22.2)	66 (7.1)
Decreased appetite	32 (14.1)	0	20 (8.6)	0	16 (11.3)	0	70 (12.5)	6 (1.1)	118(12.7)	6 (0.6)
Thrombocytopenia	14 (6.2)	4 (1.8)	2 (0.9)	1 (0.4)	15 (10.6)	1 (0.7)	86 (15.4)	38 (6.8)	115(12.4)	43 (4.6)
Asthenia	54 (23.8)	2 (0.9)	50 (21.6)	5 (2.2)	18 (12.8)	2 (1.4)	25 (4.5)	4 (0.7)	97 (10.5)	8 (0.9)
Vomiting	17 (7.5)	0	4 (1.7)	0	12 (8.5)	1 (0.7)	66 (11.8)	3 (0.5)	95 (10.2)	4 (0.4)
Diarrhoea	18 (7.9)	0	8 (3.4)	0	7 (5.0)	0	59 (10.6)	3 (0.5)	84 (9.1)	3 (0.3)
Lymphopenia	3 (1.3)	1 (0.4)	0	0	2 (1.4)	1 (0.7)	65 (11.6)	36 (6.4)	70 (7.6)	38 (4.1)
Leukopenia	3 (1.3)	1 (0.4)	0	0	4 (2.8)	1 (0.7)	60 (10.7)	13 (2.3)	67 (7.2)	15 (1.6)
Constipation	15 (6.6)	0	5 (2.2)	0	5 (3.5)	0	46 (8.2)	3 (0.5)	66 (7.1)	3 (0.3)
Neutropenia	9 (4.0)	1 (0.4)	2 (0.9)	1 (0.4)	5 (3.5)	1 (0.7)	43 (7.7)	17 (3.0)	57 (6.1)	19 (2.0)
Dysgeusia	18 (7.9)	0	3 (1.3)	0	5 (3.5)	0	20 (3.6)	0	43 (4.6)	0
Hot flush	1 (0.4)	0	14 (6.0)	0	0	0	7 (1.3)	0	8 (0.9)	0
Hypertension	0	0	17 (7.3)	5 (2.2)	0	0	7 (1.3)	5 (0.9)	7 (0.8)	5 (0.5)

Numbers (n) represent counts of patients.

Preferred terms are sorted by descending frequency in All mCRPC [177Lu]Lu-PSMA-617 Subjects 'All grades' column.

Summary of adverse events that occurred: PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of [177Lu]Lu-PSMA-617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable. VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first. AE relationship to study drug in VISION study could not make the distinction whether the AE was related to [177Lu]Lu-PSMA-617 or BSC/BSoC. MedDRA version 27.1. Source: [SCS Appendix 1-Table 5-3]

All treatment-related TEAEs by PT are found in [SCS Appendix 1-Table 5-3].

CHMP's comment:

The overall incidence of treatment-related TEAEs was approximately 85% for the AAA617 treatments across both studies and lower (63.8%) in the ARPI/ARDT arm in Study B12302. The most frequent treatment-related TEAEs observed in the AAA617 treatment arms across the studies were dry mouth, nausea, anaemia, and either asthenia (in Study B12302) or fatigue in VISION. The most frequent treatment-related TEAEs in the ARPI/ARDT arm of Study B12302 were asthenia and fatigue.

While treatment-related TEAEs were more frequent in AAA617 treatment groups, the incidence of grade ≥ 3 treatment-related TEAEs, as assessed by the investigator were generally lower in AAA617 (13.7%) and ARDT (12.1%) arms of Study B12302 than in VISION Study. This appears to be related to the earlier disease stage as illustrated by the finding that patients with more advanced disease and prior therapies in VISION had a significantly higher incidence (28.3%) of grade ≥ 3 treatment-related TEAEs. Also Grade ≥ 3 treatment-related anaemia, thrombocytopenia, and lymphopenia were reported at a higher incidence ($\geq 5.0\%$) in VISION for AAA617+BSC/BSoC arm compared to any treatment arm in Study B12302. In the ARDT arm of Study B12302, asthenia was the most frequent (2.2%) high-grade (Grade ≥ 3) treatment-related TEAE.

Median time (range) for resolution of AE was 1.30 (0.1-18.0) months for anaemia, 0.92 (0.3-16.2) months for blood creatinine increased, 0.97 (0.0-27.2) months for dry mouth, and 0.92 (0.4-9.4) months for thrombocytopenia. Median time (range) for resolution of Grade ≥ 3 AE was 0.72 (0.2-4.7) months for anaemia, 1.58 (1.6-1.6) months for dry mouth, and 0.36 (0.4-0.4) months for thrombocytopenia.

Resulting questions:

Serious TEAEs in PSMAfore occurred more often in the Control arm compared with AAA617 arm (PSMA: 20.3% versus ARDT 32.8%; Grade >3 events 18.1% versus 30.2). This appears unusual and requires an additional analysis and discussion to be informative. Although it is acknowledged that this difference was probably not cause due to the treatment directly, it may confirm insufficient treatment in the control arm due to delay of chemotherapy and thereby can be seen as a potential significant safety concern (OC).

6.3.4. Serious adverse events

Serious treatment-emergent adverse events

Serious TEAEs in PSMAfore occurred more often in the Control arm compared with AAA617 arm (PSMA: 20.3% versus ARDT 32.8%; Grade >3 events 18.1% versus 30.2).

The most frequent ($>3\%$) SOC across both studies included infections and infestations, nervous system disorders, blood and lymphatic system disorders, musculoskeletal and connective tissue disorders, renal and urinary disorders, gastrointestinal disorders, and general disorders and administration site conditions. Lower incidences of SAEs in the SOC of infections and infestations, nervous system disorders, musculoskeletal and connective tissue disorders, and renal and urinary disorders, respiratory, thoracic and mediastinal disorders, and general disorders and administration site conditions were reported in the AAA617 treatment arms than the ARPI/ARDT arm in Study B12302.

The following Table summarises the information regarding treatment-related serious treatment-emergent adverse events:

Table 2-9 Treatment-related serious adverse events occurring in at least 2 patients in either Study B12302 and Study PSMA-617-01 - by preferred term (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	9 (4.0)	8 (3.5)	6 (2.6)	6 (2.6)	5 (3.5)	2 (1.4)	53 (9.5)	48 (8.6)	67 (7.2)	58 (6.3)
Anaemia	3 (1.3)	2 (0.9)	0	0	0	0	12 (2.1)	11 (2.0)	15 (1.6)	13 (1.4)
Thrombocytopenia	1 (0.4)	1 (0.4)	0	0	0	0	5 (0.9)	5 (0.9)	6 (0.6)	6 (0.6)
Pancytopenia	0	0	0	0	0	0	5 (0.9)	5 (0.9)	5 (0.5)	5 (0.5)
Vomiting	0	0	0	0	2 (1.4)	1 (0.7)	2 (0.4)	1 (0.2)	4 (0.4)	2 (0.2)
Acute kidney injury	0	0	0	0	0	0	2 (0.4)	2 (0.4)	2 (0.2)	2 (0.2)
Constipation	0	0	0	0	0	0	2 (0.4)	2 (0.4)	2 (0.2)	2 (0.2)
Haematuria	0	0	0	0	0	0	2 (0.4)	2 (0.4)	2 (0.2)	2 (0.2)
Haemorrhage Intracranial	0	0	0	0	0	0	2 (0.4)	1 (0.2)	2 (0.2)	1 (0.1)
Leukopenia	0	0	0	0	0	0	2 (0.4)	2 (0.4)	2 (0.2)	2 (0.2)
Nausea	0	0	0	0	0	0	2 (0.4)	1 (0.2)	2 (0.2)	1 (0.1)
Pneumonia	0	0	1 (0.4)	1 (0.4)	0	0	2 (0.4)	2 (0.4)	2 (0.2)	2 (0.2)

Numbers (n) represent counts of patients.

Preferred terms are sorted by descending frequency in All mCRPC [177Lu]Lu-PSMA-617 Subjects 'All grades' column.

Summary of adverse events that occurred:

PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first. MedDRA version 27.1 Source: [SCS Appendix 1-Table 5-5]

6.3.5. Deaths and other significant events

Deaths in Study B12302 and Study PSMA-617-01 are shown below (Table 2-5):

Table 2-5 Overview of all deaths and on-treatment deaths (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227 n (%)	PSMAfore Randomised ARDT N=232 n (%)	PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141 n (%)	VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559 n (%)	All mCRPC [177Lu]Lu-PSMA-617 Patients N=927 n (%)
Category					

	PSMAfore Randomised [177Lu]Lu- PSMA-617 N=227 n (%)	PSMAfore Randomised ARDT N=232 n (%)	PSMAfore Crossover [177Lu]Lu- PSMA-617 N=141 n (%)	VISION [177Lu]Lu- PSMA-617 +BSC/BSoc N=559 n (%)	All mCRPC [177Lu]Lu- PSMA-617 Patients N=927 n (%)
All deaths	138 (60.8)	155 (66.8)	90 (63.8)	470 (84.1)	698 (75.3)
Study indication or disease progression	112 (49.3)	128 (55.2)	79 (56.0)	349 (62.4)	540 (58.3)
Other	26 (11.5)	27 (11.6)	11 (7.8)	121 (21.6)	158 (17.0)
On-treatment deaths	4 (1.8)	10 (4.3)	10 (7.1)	73 (13.1)	87 (9.4)
Study indication or disease progression	0	5 (2.2)	7 (5.0)	48 (8.6)	55 (5.9)
Other	4 (1.8)	5 (2.2)	3 (2.1)	25 (4.5)	32 (3.5)

Numbers (n) represent counts of patients.

MedDRA version 27.1

Source: [SCS Appendix 1-Table 5-21], [SCS Appendix 1-Table 5-22]

The proportion of patients who died was higher in AAA617+BSC/BSoc of VISION Study compared to AAA617 arm of Study B12302, which is attributable to the longer duration of follow-up and more advanced disease of the patient population. The proportion of patients who died was similar across the treatment arms of Study B12302.

Of-note: In VISION Study, reasons for death were recorded by the investigator on a CRF from predefined categories of disease progression, AE, unknown, or other. Only for this trial some deaths listed under the SOC 'not coded' were captured on the death CRF page under the 'other' category (corresponding to any verbatim terms provided by the investigator or 'unknown' if no additional information was provided on the CRF). For Study B12302, death due to disease progression was recorded as 'study indication'. Deaths not due to study indication (Other) include fatal adverse events and events captured outside of adverse event reporting (e.g., unrelated and occurring during the LTFU phase).

There were seven deaths under the SOC "Infection and Infestations" reported in the AAA617 arm in Study B12302, only two of them happened on-treatment, and none of the events were reported as related to AAA617.

The first on-treatment death due to infection occurred when a patient acquired fatal COVID-19 pneumonia during his hospital stay for brain metastasis (PID 5380138). The second on-treatment death was of a patient who was hospitalized and died within two weeks after his first dose of AAA617 due to sepsis, caused by urinary tract infection (PID 7377629). There was only one other sepsis related death that happened three months after the second and last dose of AAA617 was discontinued due to disease progression (PID 5310826). That patient was reported to have died of sepsis and multiorgan failure 74 days after starting docetaxel. In addition, amongst the patients who died during follow up period, there were no predisposing high-grade hematologic abnormalities observed from available laboratory values, and three deaths occurred after treatment with subsequent taxane chemotherapy.

Two cases of fatal intestinal ischemia were reported in the AAA617 arm and considered unrelated to study treatment.

- The first one (only death due to intestinal ischemia during the on-treatment period with AAA617) was in a 80 -year-old patient who received only one dose of AAA617 and then experienced grade 2 hepatic encephalopathy, not related to AAA617, leading to a liver biopsy which revealed small cell neuroendocrine carcinoma causing massive liver metastases (PID 7312416). Clinical progression was reported and treatment with AAA617 was permanently discontinued. The patient's clinical condition deteriorated rapidly, and he died on day 34 due to fatal intestinal ischemia related to his disease progression.
- The second case was of a patient in his 85 with an ongoing medical history of hypertension, gastrointestinal disorder, chronic obstructive pulmonary disease, and Respiratory, thoracic and mediastinal disorders who completed six doses of AAA617 (PID 1713664). The patient had radiographic progressive disease, presented with abdominal pain, and diagnosed with intestinal ischemia causing death 122 days after the last dose of AAA617.

CHMP's comment:

Further discussion of death events appears only meaningful with respect to trial B 12302, due to differences in LTFU.

According to the information provided, deaths in study B12302 were mostly attributed to either disease progression or to conditions commonly seen in this patient population and rather not related directly related to the treatment per se.

Deaths due to reasons other than disease progression were balanced [AAA617: 26 (11.5%) vs ARPI/ARDT: 27 (11.6%)] The most frequent primary cause for death was disease progression (AAA617: 49.3% vs ARPI/ARDT: 55.2%). Death rate in subjects who crossed over to AA617 are reported similar with 56.0% due to disease progression, while SAEs with fatal outcome were reported balances with 4 patients (1.8%) in the AAA617 arm and 5 patients (2.2%) in the ARPI/ARDT arm.

In summary, information about deathly events also does not raise significant specific concerns at present.

Resulting questions

One patient in the AAA617 arm had an event of treatment-related bone marrow failure during long-term safety follow-up, resulting in death. The applicant is requested to discuss in addition the risk for AML/MDS/Aplasia and other secondary malignancies from the totality of data currently available (also form the available post -marketing experience). (OC)

On-treatment deaths were reported in four patients (1.8%) in the AAA617 arm and in ten patients (4.3%) in the ARPI/ARDT arm. A higher incidence of fatal AEs reported under the SOC "Infections and Infestations" in the AAA617 arm compared to the ARPI/ARDT was probably caused due to the Covid-19 pandemic. It is agreed that this difference is probably not related to study treatment. Nevertheless the MAH is requested to provide more information (No of narratives) and further discuss these cases. (OC)

6.4. Safety topics of interest/ Adverse events of special interest (AESI)

STIs for AAA617 were identified based on the mechanism of action of AAA617, biological plausibility, clinical observations from Study PSMA-617-01, Health Authority feedback, and other standard topics or

potential risks. In addition, select STIs during the follow-up period were collected irrespective of causality attribution by the investigator.

STIs included the following:

- Myelosuppression
- Renal toxicity
- Dry mouth
- Dry eye
- Fractures
- Intracranial hemorrhage
- Second primary malignancies
- QT prolongation
- Hepatotoxicity
- Radiotoxicity including inadvertent exposure

The following Table summaries the results for AEs who are topics of interest:

Table 2-10 Overview of safety topics of interest (Safety set)

	PSMAfore Randomised [177Lu]Lu- PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu- PSMA-617 N=141		VISION [177Lu]Lu- PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu- PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Safety topic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dry mouth	138 (60.8)	2 (0.9)	6 (2.6)	0	74 (52.5)	0	213 (38.1)	0	425 (45.8)	2 (0.2)
Myelosuppression	89 (39.2)	30 (13.2)	55 (23.7)	20 (8.6)	57 (40.4)	15 (10.6)	263 (47.0)	130 (23.3)	409 (44.1)	175 (18.9)
Hepatotoxicity	29 (12.8)	12 (5.3)	32 (13.8)	11 (4.7)	10 (7.1) 5 (3.5)	56 (10.0)	15 (2.7)	95 (10.2)	32 (3.5)	
Dry eye	15 (6.6)	0	2 (0.9)	0	6 (4.3)	0	16 (2.9)	0	37 (4.0)	0
Fractures	9 (4.0)	2 (0.9)	20 (8.6)	12 (5.2)	5 (3.5)	1 (0.7)	32 (5.7)	12 (2.1)	46 (5.0)	15 (1.6)
QT prolongation	4 (1.8)	1 (0.4)	7 (3.0)	5 (2.2)	6 (4.3)	3 (2.1)	11 (2.0)	9 (1.6)	21 (2.3)	13 (1.4)
Second primary malignancies	4 (1.8)	2 (0.9)	3 (1.3)	2 (0.9)	2 (1.4)	0	13 (2.3)	6 (1.1)	19 (2.0)	8 (0.9)
Intracranial haemorrhage	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)	2 (1.4)	2 (1.4)	7 (1.3)	5 (0.9)	12 (1.3)	8 (0.9)
Radiotoxicity including inadvertent exposure	0	0	0	0	0	0	1(0.2)	1 (0.2)	1 (0.1)	1 (0.1)

Numbers (n) represent counts of patients.

Safety topics are sorted by descending frequency in PSMAfore [177Lu]Lu-PSMA-617 'All grades' column.

Summary of adverse events that occurred: PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first.
MedDRA version 27.1, CTCAE version V5.0, Case Retrieval Strategy version released 16Dec2024.
Source: [SCS Appendix 1-Table 5-18]

Myelosuppression, renal toxicity and secondary malignancies are most relevant in the target population the outcome for these events in trial B12302 is further detailed below in the following tables.

Myelosuppression

Table 2-12 Incidence of STI myelosuppression including preferred terms (Safety set)

Myelosuppression	PSMAfore Randomised [¹⁷⁷ Lu]Lu- PSMA-617	PSMAfore Randomised ARDT	PSMAfore Crossover [¹⁷⁷ Lu]Lu- PSMA-617	VISION [¹⁷⁷ Lu]Lu- PSMA-617 +BSC/BSoc	All mCRPC [¹⁷⁷ Lu]Lu- PSMA-617 Patients
Overall event details	N=227	N=232	N=141	N=559	N=927
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	89 (39.2)	55 (23.7)	57 (40.4)	263 (47.0)	409 (44.1)
Exposure-adjusted overall incidence, n (IR per 100 PTY)	89 (75.3)	55 (35.1)	57 (92.8)	263 (81.5)	409 (81.4)
Maximum severity grade:					
Grade 3 adverse events	23 (10.1)	18 (7.8)	14 (9.9)	108 (19.3)	145 (15.6)
Grade 4 adverse events	7 (3.1)	2 (0.9)	1 (0.7)	19 (3.4)	27 (2.9)
Grade 5 adverse events	0	0	0	3 (0.5)	3 (0.3)
Serious adverse events	7 (3.1)	3 (1.3)	1 (0.7)	30 (5.4)	38 (4.1)
Treatment-related adverse events	61 (26.9)	12 (5.2)	47 (33.3)	225 (40.3)	333 (35.9)
Action taken:					
Drug withdrawn	6 (2.6)	0	3 (2.1)	39 (7.0)	48 (5.2)
Dose reduced	4 (1.8)	1 (0.4)	7 (5.0)	23 (4.1)	34 (3.7)
Drug interrupted	9 (4.0)	5 (2.2)	8 (5.7)	52 (9.3)	69 (7.4)
Dose not changed/NA/Unknown	86 (37.9)	53 (22.8)	53 (37.6)	244 (43.6)	383 (41.3)
AE outcome:					
Recovered/resolved	46 (20.3)	31 (13.4)	30 (21.3)	130 (23.3)	206 (22.2)
Recovering/resolving	15 (6.6)	6 (2.6)	11 (7.8)	4 (0.7)	30 (3.2)
Not recovered/not resolved	54 (23.8)	27 (11.6)	36 (25.5)	201 (36.0)	291 (31.4)
Recovered/resolved with sequelae	1 (0.4)	1 (0.4)	0	3 (0.5)	4 (0.4)
Fatal	0	0	0	3 (0.5)	3 (0.3)
Unknown	2 (0.9)	1 (0.4)	0	4 (0.7)	6 (0.6)
Preferred terms:					
Anaemia	62 (27.3)	45 (19.4)	39 (27.7)	179 (32.0)	280 (30.2)
Thrombocytopenia	18 (7.9)	7 (3.0)	17 (12.1)	95 (17.0)	130 (14.0)
Lymphopenia	4 (1.8)	0	3 (2.1)	80 (14.3)	87 (9.4)

Myelosuppression	PSMAfore Randomised [¹⁷⁷Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [¹⁷⁷Lu]Lu- PSMA-617 N=141	VISION [¹⁷⁷Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [¹⁷⁷Lu]Lu- PSMA-617 Patients N=927
Overall event details	N=227	N=232	N=141	N=559	N=927
	n (%)	n (%)	n (%)	n (%)	n (%)
Leukopenia	5 (2.2)	0	4 (2.8)	69 (12.3)	78 (8.4)
Neutropenia	13 (5.7)	2 (0.9)	6 (4.3)	45 (8.1)	64 (6.9)
Lymphocyte count decreased	12 (5.3)	3 (1.3)	5 (3.5)	0	17 (1.8)
Platelet count decreased	6 (2.6)	2 (0.9)	7 (5.0)	0	13 (1.4)
Pancytopenia	1 (0.4)	1 (0.4)	2 (1.4)	8 (1.4)	11 (1.2)
White blood cell count decreased	9 (4.0)	3 (1.3)	2 (1.4)	0	11 (1.2)
Neutrophil count decreased	3 (1.3)	3 (1.3)	4 (2.8)	0	7 (0.8)
Febrile neutropenia	2 (0.9)	0	1 (0.7)	2 (0.4)	5 (0.5)
Haemoglobin decreased	2 (0.9)	1 (0.4)	1 (0.7)	0	3 (0.3)
Bicytopenia	0	0	0	1 (0.2)	1 (0.1)
Bone marrow failure	0	0	0	1 (0.2)	1 (0.1)
Normocytic anaemia	0	0	0	1 (0.2)	1 (0.1)

Renal toxicity

Table 2-13 Incidence of STI renal toxicity including preferred terms (Safety set)

Renal toxicity	PSMAfore Randomised [¹⁷⁷Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [¹⁷⁷Lu]Lu- PSMA-617 N=141	VISION [¹⁷⁷Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [¹⁷⁷Lu]Lu- PSMA-617 Patients N=927
Overall event details	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	14 (6.2)	19 (8.2)	9 (6.4)	54 (9.7)	77 (8.3)
Exposure-adjusted overall incidence, n (IR per 100 PTY)	14 (9.3)	19 (10.7)	9 (11.2)	54 (12.0)	77 (11.3)
Maximum severity grade:					
Grade 3 adverse events	2 (0.9)	7 (3.0)	2 (1.4)	19 (3.4)	23 (2.5)
Grade 4 adverse events	0	1 (0.4)	0	0	0
Serious adverse events	2 (0.9)	6 (2.6)	3 (2.1)	10 (1.8)	15 (1.6)
Treatment-related adverse events	7 (3.1)	0	2 (1.4)	22 (3.9)	31 (3.3)
Action taken:					
Drug withdrawn	0	0	0	1 (0.2)	1 (0.1)
Dose reduced	0	1 (0.4)	0	2 (0.4)	2 (0.2)
Drug interrupted	2 (0.9)	1 (0.4)	0	2 (0.4)	4 (0.4)
Dose not changed/NA/Unknown	13 (5.7)	17 (7.3)	9 (6.4)	50 (8.9)	72 (7.8)
AE outcome:					
Recovered/resolved	13 (5.7)	13 (5.6)	6 (4.3)	32 (5.7)	51 (5.5)
Recovering/resolving	1 (0.4)	0	2 (1.4)	1 (0.2)	4 (0.4)
Not recovered/not resolved	3 (1.3)	6 (2.6)	1 (0.7)	23 (4.1)	27 (2.9)

Renal toxicity	PSMAfore Randomised [177Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [177Lu]Lu- PSMA-617 N=141	VISION [177Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [177Lu]Lu- PSMA-617 Patients N=927
Overall event details	n (%)	n (%)	n (%)	n (%)	n (%)
Fatal	0	0	0	0	0
Unknown	0	0	0	1 (0.2)	1 (0.1)
Preferred terms:					
Blood creatinine increased	10 (4.4)	7 (3.0)	5 (3.5)	33 (5.9)	48 (5.2)
Acute kidney injury	4 (1.8)	10 (4.3)	2 (1.4)	20 (3.6)	26 (2.8)
Renal failure	2 (0.9)	3 (1.3)	0	1 (0.2)	3 (0.3)
Blood urea increased	1 (0.4)	0	0	1 (0.2)	2 (0.2)
Renal impairment	0	0	1 (0.7)	1 (0.2)	2 (0.2)
Anuria	0	0	1 (0.7)	0	1 (0.1)
Glomerular filtration rate decreased	0	0	0	1 (0.2)	1 (0.1)
Oliguria	0	0	1 (0.7)	0	1 (0.1)
Proteinuria	0	0	0	1 (0.2)	1 (0.1)
Urine output decreased	0	0	0	1 (0.2)	1 (0.1)

n represent counts of patients. A patient may be counted in several rows for action taken and outcome Summary of AEs that occurred:

PSMAfore: on or after first dose of study treatment to earlier of below dates: 1.) latest of end of treatment disposition date+30 days or (last dose of ARDT+30 days or last dose date of AAA617+41 days), as applicable; 2.) day before start of crossover treatment, if applicable.

VISION: from date of initiation of randomised treatment up to 30 days after date of last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first. IR=exposure-adjusted incidence rate: number of patients with an event divided by corresponding sum of exposure duration for all patients, where duration of exposure in Patient Treatment Years (PTY) is counted up to the first qualifying event (or end of on-treatment period for patients without event).

MedDRA version 27.1, CTCAE version V5.0, Case Retrieval Strategy version 16Dec2024

Source: [SCS Appendix 1-Table 5-19]

Second primary malignancies

Table 2-14 Incidence of STI second primary malignancies including preferred terms (Safety set)

	PSMAfore Randomised [177Lu]Lu- PSMA-617 N=227	PSMAfore Randomised ARDT N=232	PSMAfore Crossover [177Lu]Lu- PSMA-617 N=141	VISION [177Lu]Lu- PSMA-617 +BSC/BSoc N=559	All mCRPC [177Lu]Lu- PSMA-617 Patients N=927
Second primary malignancies	PSMA-617	ARDT	PSMA-617	+BSC/BSoc	Patients
Overall event details	N=227	N=232	N=141	N=559	N=927
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	4 (1.8)	3 (1.3)	2 (1.4)	13 (2.3)	19 (2.0)
Exposure-adjusted overall incidence, n (IR per 100 PTY)	4 (2.6)	3 (1.6)	2 (2.4)	13 (2.8)	19 (2.7)
Maximum severity grade:					
Grade 3 adverse events	2 (0.9)	2 (0.9)	0	4 (0.7)	6 (0.6)
Grade 4 adverse events	0	0	0	1 (0.2)	1 (0.1)
Grade 5 adverse events	0	0	0	1 (0.2)	1 (0.1)
Serious adverse events	4 (1.8)	3 (1.3)	2 (1.4)	4 (0.7)	10 (1.1)
Treatment-related adverse events	0	0	0	1 (0.2)	1 (0.1)
Action taken:					
Drug withdrawn	0	0	0	1 (0.2)	1 (0.1)

	PSMAfore Randomised [177Lu]Lu- PSMA-617	PSMAfore Randomised ARDT	PSMAfore Crossover [177Lu]Lu- PSMA-617	VISION [177Lu]Lu- PSMA-617 +BSC/BSOC	All mCRPC [177Lu]Lu- PSMA-617 Patients
Second primary malignancies	N=227	N=232	N=141	N=559	N=927
Overall event details	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred term					
Dose reduced	0	0	0	0	0
Drug interrupted	1 (0.4)	1 (0.4)	0	0	1 (0.1)
Dose not changed/NA/Unknown	3 (1.3)	2 (0.9)	2 (1.4)	12 (2.1)	17 (1.8)
AE outcome:					
Recovered/resolved	2 (0.9)	3 (1.3)	2 (1.4)	5 (0.9)	9 (1.0)
Recovering/resolving	0	0	0	0	0
Not recovered/not resolved	2 (0.9)	1 (0.4)	0	5 (0.9)	7 (0.8)
Recovered/resolved with sequelae	0	0	0	1 (0.2)	1 (0.1)
Fatal	0	0	0	1 (0.2)	1 (0.1)
Unknown	0	0	0	1 (0.2)	1 (0.1)
Preferred terms:					
Squamous cell carcinoma	0	0	0	4 (0.7)	4 (0.4)
Basal cell carcinoma	1 (0.4)	1 (0.4)	1 (0.7)	1 (0.2)	3 (0.3)
Adenocarcinoma of colon	1 (0.4)	0	0	1 (0.2)	2 (0.2)
Malignant melanoma	0	0	1 (0.7)	1 (0.2)	2 (0.2)
Metastases to central nervous system*	0	0	0	2 (0.4)	2 (0.2)
Metastases to meninges	0	0	0	2 (0.4)	2 (0.2)
Clear cell renal cell carcinoma	1 (0.4)	0	0	0	1 (0.1)
Pancreatic carcinoma	0	0	0	1 (0.2)	1 (0.1)
Renal cell carcinoma	1 (0.4)	0	0	0	1 (0.1)
Squamous cell carcinoma of skin	0	0	0	1 (0.2)	1 (0.1)
Leiomyosarcoma	0	1 (0.4)	0	0	0
Leiomyosarcoma metastatic	0	1 (0.4)	0	0	0
Transitional cell carcinoma	0	1 (0.4)	0	0	0

n=represent counts of patients. A patient may be counted in several rows for action taken and outcome Summary of AEs that occurred:

PSMAfore: on or after first dose of study treatment to earlier of below dates: 1.) latest of end of treatment disposition date+30 days or (last dose of ARDT+30 days or last dose date of AAA617+41 days), as applicable; 2.) day before start of crossover treatment, if applicable.

VISION: from date of initiation of randomised treatment up to 30 days after date of last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first.

*Metastases to central nervous system did not qualify for second malignancy in Study B12302.

IR=exposure-adjusted incidence rate: number of patients with an event divided by corresponding sum of exposure duration for all patients, where duration of exposure in Patient Treatment Years (PTY) is counted up to the first qualifying event (or end of on-treatment period for patients without event).

MedDRA version 27.1, CTCAE version V5.0, Case Retrieval Strategy version 16Dec2024

Source: [SCS Appendix 1-Table 5-19]

6.4.1. Long-term safety from Study B12302

An overview of AEs reported during the (post-treatment) LTFU period in Study B12302 is shown in [Table 4-2](#).

Table 4-2 Overview of AEs during long-term follow-up in Study B12302 (Lu- PSMA-617 safety set)

	Randomised [¹⁷⁷ Lu]Lu-PSMA- 617 Patients N=227		Crossover [¹⁷⁷ Lu]Lu-PSMA-617 Patients N=141		All [¹⁷⁷ Lu]Lu-PSMA-617 Patients N=368	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse events	83 (36.6)	35 (15.4)	43 (30.5)	19 (13.5)	126 (34.2)	54 (14.7)
Treatment-related AEs	26 (11.5)	10 (4.4)	11 (7.8)	4 (2.8)	37 (10.1)	14 (3.8)
Serious adverse events	16 (7.0)	14 (6.2)	6 (4.3)	5 (3.5)	22 (6.0)	19 (5.2)
Treatment-related SAEs	3 (1.3)	3 (1.3)	1 (0.7)	1 (0.7)	4 (1.1)	4 (1.1)
Fatal adverse events	1 (0.4)	1 (0.4)	2 (1.4)	2 (1.4)	3 (0.8)	3 (0.8)
Treatment-related fatal AEs	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)

Numbers (n) represent counts of patients.

Adverse events that occurred after latest of end of randomised treatment disposition date + 30 days or end of crossover treatment disposition date + 30 days or last dose date of [¹⁷⁷Lu]Lu-PSMA-617 + 41 days are summarized. MedDRA version 27.1, CTCAE version V5.0.

DCO: 01Jan2025

Source: [Study B12302 IA4-Table 14.3.1-3.28]

AEs reported in two or more patients during the LTFU period in Study B12302 are shown in ([Table 4-3](#)).

Table 4-3 Adverse events in 2 or more patients by preferred term during long- term follow-up in Study B12302 (Lu-PSMA-617 safety set)

	Randomised [177Lu]Lu-PSMA- 617 Patients N=227		Crossover [177Lu]Lu-PSMA- 617 Patients N=141		All [177Lu]Lu-PSMA- 617 Patients N=368	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one event	83 (36.6)	35 (15.4)	43 (30.5)	19 (13.5)	126 (34.2)	54 (14.7)
Anaemia	41 (18.1)	15 (6.6)	22 (15.6)	7 (5.0)	63 (17.1)	22 (6.0)
Thrombocytopenia	12 (5.3)	7 (3.1)	6 (4.3)	1 (0.7)	18 (4.9)	8 (2.2)
Dry mouth	9 (4.0)	0	4 (2.8)	0	13 (3.5)	0
Lymphocyte count decreased	9 (4.0)	7 (3.1)	2 (1.4)	2 (1.4)	11 (3.0)	9 (2.4)
Platelet count decreased	3 (1.3)	0	6 (4.3)	1 (0.7)	9 (2.4)	1 (0.3)
Arthralgia	4 (1.8)	0	3 (2.1)	0	7 (1.9)	0
Neutropenia	5 (2.2)	3 (1.3)	1 (0.7)	1 (0.7)	6 (1.6)	4 (1.1)
Blood creatinine increased	3 (1.3)	0	2 (1.4)	0	5 (1.4)	0
Dyspnoea	4 (1.8)	1 (0.4)	1 (0.7)	0	5 (1.4)	1 (0.3)
Fatigue	3 (1.3)	1 (0.4)	2 (1.4)	1 (0.7)	5 (1.4)	2 (0.5)
Leukopenia	2 (0.9)	0	3 (2.1)	2 (1.4)	5 (1.4)	2 (0.5)
Blood ALP increased	2 (0.9)	2 (0.9)	2 (1.4)	1 (0.7)	4 (1.1)	3 (0.8)
Constipation	3 (1.3)	0	1 (0.7)	0	4 (1.1)	0
Lymphopenia	3 (1.3)	2 (0.9)	1 (0.7)	1 (0.7)	4 (1.1)	3 (0.8)
Acute kidney injury	1 (0.4)	1 (0.4)	2 (1.4)	1 (0.7)	3 (0.8)	2 (0.5)
Sepsis	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.7)	3 (0.8)	3 (0.8)
Back pain	2 (0.9)	0	0	0	2 (0.5)	0
Basal cell carcinoma	0	0	2 (1.4)	1 (0.7)	2 (0.5)	1 (0.3)
Chronic kidney disease	2 (0.9)	0	0	0	2 (0.5)	0
Febrile neutropenia	2 (0.9)	1 (0.4)	0	0	2 (0.5)	1 (0.3)
Haematuria	2 (0.9)	0	0	0	2 (0.5)	0
Nausea	2 (0.9)	0	0	0	2 (0.5)	0
Pancytopenia	2 (0.9)	2 (0.9)	0	0	2 (0.5)	2 (0.5)
Pyrexia	2 (0.9)	0	0	0	2 (0.5)	0
Syncope	0	0	2 (1.4)	1 (0.7)	2 (0.5)	1 (0.3)
Weight decreased	1 (0.4)	0	1 (0.7)	0	2 (0.5)	0

Numbers (n) represent counts of patients.

Adverse events that occurred after latest of end of randomised treatment disposition date + 30 days or end of crossover treatment disposition date + 30 days or last dose date of [177Lu]Lu-PSMA-617 + 41 days are summarized.

MedDRA version 27.1, CTCAE version V5.0.

Source: [Study B12302 IA4-Table 14.3.1-3.29]

SAEs related to AAA617 by SOC and PT during long-term follow-up in Study B12302 are shown in [Table 4-4](#).

Table 4-4 AAA617-related SAEs by system organ class and preferred term during long-term follow-up in Study B12302 (Lu-PSMA-617 safety set)

	Randomised [177Lu]Lu-PSMA- 617 Patients N=227		Crossover [177Lu]Lu-PSMA- 617 Patients N=141		All [177Lu]Lu-PSMA- 617 Patients N=368	
System organ class	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of subjects with at least one event	3 (1.3)	3 (1.3)	1 (0.7)	1 (0.7)	4 (1.1)	4 (1.1)
Blood and lymphatic system disorders	2 (0.9)	2 (0.9)	1 (0.7)	1 (0.7)	3 (0.8)	3 (0.8)
Anaemia	0	0	1 (0.7)	1 (0.7)	1 (0.3)	1 (0.3)
Bone marrow failure	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)
Pancytopenia	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)
Thrombocytopenia	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)
Dyspnoea	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)

Numbers (n) represent counts of patients.

Adverse events that occurred after latest of end of randomised treatment disposition date + 30 days or end of crossover treatment disposition date + 30 days or last dose date of [177Lu]Lu-PSMA-617 + 41 days are summarized.

MedDRA version 27.1, CTCAE version V5.0.

Source: [Study B12302 IA4-Table 14.3.1-3.19]

An overview of AEs meeting the STI definitions during the long-term follow-up in Study B12302 is shown in [Table 4-5](#).

Table 4-5 Overview of safety topics of interest during long-term follow-up in Study B12302 (Lu-PSMA-617 safety set)

	Randomised [177Lu]Lu-PSMA-617 Patients N=227	Crossover [177Lu]Lu-PSMA- 617 Patients N=141	All [177Lu]Lu-PSMA- 617 Patients N=368
Safety topic	n (%)	n (%)	n (%)
Dry mouth	9 (4.0)	4 (2.8)	13 (3.5)
Myelosuppression	53 (23.3)	28 (19.9)	81 (22.0)
Renal toxicity	5 (2.2)	4 (2.8)	9 (2.4)
Dry eye	0	0	0
Second primary malignancies	1 (0.4)	2 (1.4)	3 (0.8)

Numbers (n) represent counts of patients.

Adverse events that occurred after latest of end of randomised treatment disposition date + 30 days or end of crossover treatment disposition date + 30 days or last dose date of [177Lu]Lu-PSMA-617 + 41 days are summarized.

MedDRA version 27.1, CTCAE version V5.0. Case Retrieval Strategy version released Dec162024.

Source: [Study B12302 IA4-Table 14.3.1-3.30]

6.5. Safety in special populations

Subgroups were analysed according to age, race, baseline eGFR levels, baseline liver parameters, and region.

Subgroup analyses of adverse events by age

The profile of AEs by age group categories < 65 years, ≥ 65 to < 75 years, and ≥ 75 years was generally similar across treatment arms 1-Table 5-7a]. In particular, treatment with AAA617 did not appear to increase the differences in the incidence of TEAEs between the age groups with respect to the frequencies of TEAEs and high- grade (Grade ≥3) TEAEs with increasing age .

Subgroup analyses adverse events by geographical regions and race

Study B12302 enrolled predominantly patients from Europe whereas Study VISION trial (PSMA-617-01) enrolled predominantly patients from North America. Therefore, the subgroups by geographical region reflect predominantly the differences between the two studies.

Moreover, approximately 90% of the included patients were White, thus this analysis remains less informative due to the low sample size in race subgroups other than White. However, the data presented indicates no relevant safety difference according to race.

6.6. Laboratory findings

Hematology

Worsening values from baseline for hematology abnormalities are presented in the table below.

Across most treatment arms, the most frequent worst post-baseline hematology abnormalities were low lymphocyte and hemoglobin levels. Hematology abnormal decreases were more frequent in the AAA617 arms than in the ARPI/ARDT arm in Study B12302.

Almost all patients had normal (grade 0), or low-grade hematology abnormalities (grade 1 or 2) at baseline for all hematology parameters analyzed based on CTCAE grades.

Table 3-1 Worst post-baseline haematology abnormalities based on CTCAE grades (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoC N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Parameter abnormality	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin (g/L), Blood- Decreased	211 (93.0)	15 (6.6)	168 (72.4)	17 (7.3)	134 (95.0)	10 (7.1)	546 (97.7)	82 (14.7)	891 (96.1)	107 (11.5)
Hemoglobin (g/L), Blood- Increased	0	0	1 (0.4)	0	0	0	1 (0.2)	0	1 (0.1)	0
Leukocytes (10 ⁹ /L), Blood- Decreased	128 (56.4)	10 (4.4)	63 (27.2)	4 (1.7)	78 (55.3)	3 (2.1)	317 (56.7)	38 (6.8)	523 (56.4)	51 (5.5)
Lymphocytes (10 ⁹ /L), Blood- Decreased	221 (97.4)	64 (28.2)	209 (90.1)	30 (12.9)	138 (97.9)	38 (27.0)	508 (90.9)	277 (49.6)	867 (93.5)	379 (40.9)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSMAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Parameter abnormality	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lymphocytes (109/L), Blood-Increased	3 (1.3)	0	3 (1.3)	0	1 (0.7)	0	2 (0.4)	2 (0.4)	6 (0.6)	2 (0.2)
Neutrophils (109/L), Blood-Decreased	88 (38.8)	8 (3.5)	46 (19.8)	3 (1.3)	53 (37.6)	4 (2.8)	156 (27.9)	25 (4.5)	297 (32.0)	37 (4.0)
Platelets (109/L), Blood-Decreased	72 (31.7)	6 (2.6)	31 (13.4)	4 (1.7)	49 (34.8)	2 (1.4)	269 (48.1)	50 (8.9)	390 (42.1)	58 (6.3)

Numbers (n) represent counts of patients.

'All grades' represents patients with any grade 1, 2, 3 or 4 post-baseline. Post-baseline assessments are those that occurred:

PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first.

Grades based on CTCAE version V5.0.

Across most treatment arms, the most frequent worst post-baseline hematology abnormalities were low lymphocyte and hemoglobin levels. Hematology abnormal decreases were more frequent in the AAA617 arms than in the ARPI/ARDT arm in Study B12302.

Almost all patients had normal (grade 0), or low-grade hematology abnormalities (grade 1 or 2) at baseline for all hematology parameters analyzed based on CTCAE grades.

Across the treatment arms in the pooled safety dataset, the median time to first occurrence of a CTCAE grade ≥ 1 hematological event of hemoglobin decreased, neutrophils decreased, and lymphocytes decreased was 1.08 months (range: 0.2-19.4), 1.87 months (range: 0.2-25.3) and 0.43 months (range: 0.0-8.3), respectively [SCS Appendix 1-Table 3-9].

Across the treatment arms in the pooled safety dataset, the median time to first occurrence of a CTCAE Grade 3 or 4 hematological event of hemoglobin decreased, neutrophils decreased, and lymphocytes decreased was 3.71 months (range: 0.3-18.3), 3.94 months (range: 0.2-10.7) and 1.91 months (range: 0.0-18.0) months, respectively [SCS Appendix 1-Table 3-10].

In Study B12302, for the PSMAfore safety set, the median time to first occurrence in the AAA617 arm of a CTCAE Grade 3 or 4 event of hemoglobin decreased, neutrophils decreased, and lymphocytes decreased was 3.61 months (range: 0.3-9.3), 4.99 months (range: 2.0-8.3) months and 4.14 months (range: 0.2-10.1), respectively [Study B12302 IA4-Table 14.3-2.9].

In Study B12302, for the PSMAfore safety set, the median time to resolution of a CTCAE grade ≥ 3 hematological event of hemoglobin decreased, neutrophils decreased, and lymphocytes decreased was 1.26 months (range: 0.2-6.5), 1.02 months (range: 0.1-2.7) and 1.53 months (range: 0.3-23.4).

Clinical chemistry

Across all treatment arms in the pooled safety dataset, the most frequent worst post-baseline clinical chemistry abnormalities were decreased eGFR (87.6%) and increased serum alkaline phosphatase level (38.0%) ([Table 3-2](#)).

Table 3-2 Worst post-baseline biochemistry abnormalities based on CTCAE grades (Safety set)

	PSMAfore Randomised [177Lu]Lu-PSMA-617 N=227		PSMAfore Randomised ARDT N=232		PSAfore Crossover [177Lu]Lu-PSMA-617 N=141		VISION [177Lu]Lu-PSMA-617 +BSC/BSoc N=559		All mCRPC [177Lu]Lu-PSMA-617 Patients N=927	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Parameter - abnormality	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine Aminotransferase (U/L), Serum-Increased	30 (13.2)	2 (0.9)	20 (8.6)	4 (1.7)	21 (14.9)	2 (1.4)	106 (19.0)	8 (1.4)	157 (16.9)	12 (1.3)
Albumin (g/L), Serum- Decreased	14 (6.2)	0	27 (11.6)	0	8 (5.7)	0	245 (43.8)	3 (0.5)	267 (28.8)	3 (0.3)
Alkaline Phosphatase (U/L), Serum-Increased	113 (49.8)	23 (10.1)	157 (67.7)	31 (13.4)	88 (62.4)	25 (17.7)	151 (27.0)	4 (0.7)	352 (38.0)	52 (5.6)
Aspartate Aminotransferase (U/L), Serum-Increased	50 (22.0)	4 (1.8)	44 (19.0)	3 (1.3)	33 (23.4)	4 (2.8)	179 (32.0)	6 (1.1)	262 (28.3)	14 (1.5)
Bilirubin (μmol/L), Serum- Increased	10 (4.4)	1 (0.4)	17 (7.3)	1 (0.4)	7 (5.0)	1 (0.7)	54 (9.7)	4 (0.7)	71 (7.7)	6 (0.6)
Calcium Corrected (mmol/L), Serum- Decreased	41 (18.1)	2 (0.9)	27 (11.6)	2 (0.9)	27 (19.1)	2 (1.4)	217 (38.8)	11 (2.0)	285 (30.7)	15 (1.6)
Calcium Corrected (mmol/L), Serum-Increased	7 (3.1)	0	18 (7.8)	0	5 (3.5)	0	86 (15.4)	2 (0.4)	98 (10.6)	2 (0.2)
Creatinine (μmol/L), Serum or Plasma-Increased	24 (10.6)	0	39 (16.8)	3 (1.3)	19 (13.5)	2 (1.4)	168 (30.1)	5 (0.9)	211 (22.8)	7 (0.8)
Estimated Glomerular Filtration Rate (mL/min/1.73m2)-Decreased	226 (99.6)	2 (0.9)	231 (99.6)	9 (3.9)	141 (100)	5 (3.5)	445 (79.6)	20 (3.6)	812 (87.6)	27 (2.9)
Glucose (mmol/L), Serum- Decreased	7 (3.1)	0	11 (4.7)	1 (0.4)	5 (3.5)	0	60 (10.7)	1 (0.2)	72 (7.8)	1 (0.1)
Potassium (mmol/L), Serum or Plasma- Decreased	16 (7.0)	2 (0.9)	46 (19.8)	6 (2.6)	16 (11.3)	1 (0.7)	92 (16.5)	7 (1.3)	124 (13.4)	10 (1.1)
Potassium (mmol/L), Serum or Plasma-Increased	31 (13.7)	1 (0.4)	37 (15.9)	2 (0.9)	31 (22.0)	2 (1.4)	149 (26.7)	6 (1.1)	211 (22.8)	9 (1.0)
Sodium (mmol/L), Serum or Plasma- Decreased	28 (12.3)	0	50 (21.6)	0	31 (22.0)	0	208 (37.2)	4 (0.7)	267 (28.8)	4 (0.4)
Sodium (mmol/L), Serum or Plasma-Increased	47 (20.7)	0	53 (22.8)	0	32 (22.7)	0	62 (11.1)	0	141 (15.2)	0

Numbers (n) represent counts of patients. 'All grades' represents patients with any grade 1, 2, 3 or 4 post-baseline. Post-baseline assessments are those that occurred:

PSMAfore study: on or after first dose of study treatment to the earlier of below dates: 1.) latest of end of treatment disposition date + 30 days or (last dose date of ARDT + 30 days or last dose date of AAA617 + 41 days), as applicable; 2.) the day before start of crossover treatment, if applicable.

VISION study: from the date of initiation of randomised treatment up to 30 days after the date of the last administration of randomised treatment or the day prior to the initiation of subsequent anti-cancer treatment, whichever occurs first.

Grades based on CTCAE version V5.0. Source: [SCS Appendix 1-Table 3-2]

CHMP's comment:

Incidences of clinical chemistry abnormal increases/decreases were similar in the AAA617 arm and ARPI/ARDT arm in Study B12302 and higher in the AAA617+BSC/BSoC arm of the VISION Study, with the exception of albumin decreased, ALP increased, calcium corrected decreased and sodium decreased which have a >20% difference between the AAA617 arm of Study B12302 and the AAA617+BSC/BSoC arm of Study PSMA-617-01. However, these differences are likely to reflect more the impact of the later treatment line than intrinsic safety differences between the approved and the applied population.

It is noted that in Trial B12302 the frequency of ALP was significantly higher than in VISION trial (ALP: AAA617: 49.8%, ARPI/ARDT: 67.7% versus VISION: 27.1 %). This difference occurs also with respect to the ALP increased Grade ≥ 3 and needs further clarification (OC). Moreover, one patient in the randomised AAA617 treatment arm of Study B12302 had a constellation of values suggestive of potential Hy's law during the randomised treatment. However, the abnormalities in liver parameters in this patient were explained by the rapidly progressive liver metastasis in this patient and thereby may explain this event. Since DILI is mostly caused due to drugs undergoing metabolism, which is not the case in AAA617, it appears rather unlikely that AAA617 has significantly contributed to this event.

With respect to renal function, the results for creatinine increased in arm B12302 were slightly lower in the AAA617 compared with control arm (AAA617: 10.6% vs ARPI/ARDT : 16.8%), both rates were lower than the 30.1% observed in VISION for AAA617 and again may reflect a difference between the first line and more advanced mCRPC population. Nevertheless, in the context of renal function it remains counterintuitive that decreased eGFR rate was significantly higher in both arms of B12302 (both 99.6%) compared with VISION 79.6%. The applicant is requested to clarify whether there is any explanation for this outcome.

Resulting questions:

It is noted that in Trial B12302 the frequency of ALP was significantly higher than in VISION trial (ALP: AAA617: 49.8%, ARPI/ARDT: 67.7% versus VISION: 27.1 %). This difference occurs also with respect to the ALP increased Grade ≥ 3 and needs further clarification (OC). The MAH is requested to interpret this outcome (OC).

With respect to renal function, the results for creatinine increased in arm B12302 were slightly lower in the AAA617 compared with control arm (AAA617: 10.6% vs ARPI/ARDT : 16.8%), both rates were lower than the 30.1% observed in VISION for AAA617 and again may reflect a difference between the first line and more advanced mCRPC population. Nevertheless, in the context of renal function it remains counterintuitive that decreased eGFR rate was significantly higher in both arms of B12302 (both 99.6%) compared with VISION 79.6%. The applicant is requested to clarify whether there is any explanation for this outcome (OC).

Vital signs, physical findings, and other observations related to safety

Across the treatment arms of the pooled safety dataset, vital signs, physical findings, and other observations were generally consistent between the studies.

Vital signs: Analyses of the pooled safety dataset showed no clinically relevant changes. Notable vital signs were typically observed in < 10% of the patients, except for decreased weight by $\geq 10\%$ from baseline, observed in approximately 10-15% patients across treatment arms.

Electrocardiograms: None of the ECG results have raised any specific safety concerns. ECG abnormalities were mostly less frequent in the AAA617 arm compared to the ARPI/ARDT arm and there remains no clear association between AAA617 and conduction abnormalities [Study B12302 IA3-Section 12.7.2].

6.7. Dosimetry

Kidney safety dosimetry

The safety dosimetry assessments of the kidneys in 5 German patients were evaluated in Study B12302, as described in the protocol [Study B12302-Appendix 16.1.1-Section 8.5.3]. The mean kidney time activity curve after a single cycle in Study B12302 is presented in the dosimetry report. The mean absorbed dose to the kidneys after a single cycle of treatment was found to be 0.51 ± 0.15 Gy/GBq. The estimated cumulative dose incurred after a full 6 cycle of treatment was 22.5 ± 6.7 Gy.

The mean kidney time activity curve and the mean absorbed dose to the kidneys after a single cycle of treatment are comparable for both studies [SCS Appendix 1-Figure 8-1] and [SCS Appendix 1-Figure 8-2]

The mean absorbed dose to the kidney after a single cycle of treatment was 0.51 ± 0.15 Gy/GBq and 0.42 ± 0.19 Gy/GBq in Study B12302 and PSMA-617-01 sub-study, respectively.

CHMP's comment

A comparison with dosimetry results in the VISION trial remains missing and should be provided to assess the renal safety risk in the new target population.

Resulting question

No comparison with dosimetry results in the VISION trial was provided. The applicant is requested to provide this information to assess whether any difference in renal safety risk has to be expected in the newly applied target population (OC).

6.8. Safety related to drug-drug interactions and other interactions

There are no known drug interactions with vipivotide tetraxetan. Vipivotide tetraxetan is unlikely to have any metabolic- or transporter-mediated drug interactions in vivo.

Vipivotide tetraxetan is not a substrate of cytochrome P450 (CYP450) enzymes. It does not induce cytochrome P450 (CYP) 1A2, 2B6 or 3A4, and it does not inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 in vitro.

Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2, and it is not an inhibitor of BCRP, P-gp, BSEP, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 in vitro.

6.9. Discontinuation due to adverse events

Adverse events leading to discontinuation of study treatment

The most frequent TEAEs leading to discontinuation in the AAA617 treatment arms of the pooled safety dataset were in the SOC blood and lymphatic system disorders, with most frequent PT thrombocytopenia.

The incidence of TEAEs leading to discontinuation within this SOC was lower in all treatment arms of Study B12302 compared to the AAA617+BSC/BSoc arm of Study PSMA-617-01.

In the ARPI/ARDT arm of Study B12302, the most frequent TEAEs leading to discontinuation were in the SOC nervous system disorders with most frequent PT spinal cord compression.

Adverse events leading to dose adjustment

Dose adjustment was allowed for safety concerns at the discretion of the treating investigator, and per dose modification guidelines presented in the study protocol.

All TEAEs leading to dose adjustment by SOC and PT are given in [SCS Appendix 1-Table 5- 12]. The incidence of TEAEs leading to study treatment dose adjustment (5.4%) and high-grade (Grade ≥ 3) TEAEs leading to dose adjustment (1.9%) were generally low.

The ARPI/ARDT arm showed higher incidence than all AAA617 treatment arms, which might be somewhat influenced by the less frequent dosing interval for AAA617 (once every 6 weeks) compared to that of ARPI/ARDT (daily), giving the patients in the AAA617 treatment arms in Study B12302 more time to recover from TEAEs before their next dose without needing dose reduction.

AS regarding treatment discontinuation, the most frequent TEAEs leading to dose adjustment in the AAA617 treatment arms of the pooled safety dataset were in the SOC blood and lymphatic system disorders (3.3%). The most frequent PTs leading to dose adjustment within this SOC for the pooled safety dataset were thrombocytopenia (1.3%) and anaemia (1.2%).

In the ARPI/ARDT arm of Study B12302, the most frequent TEAEs leading to dose adjustment were in the SOC general disorders and administration site conditions (9.1%), with most frequent PTs asthenia (4.3%) and fatigue (4.7%), which were reported with lower incidence in the AAA617+BSC/BSoc arm of Study PSMA-617-01 or in the AAA617 arms of Study B12302.

Across the AAA617 treatment arms in the pooled safety dataset, the most frequent Grade ≥ 3 TEAEs leading to dose adjustment were anaemia and leukopenia (0.5%). In the ARPI/ARDT arm of Study B12302, the most frequent Grade ≥ 3 TEAEs leading to dose adjustment was asthenia (0.9%) and hypertension (0.9%).

Adverse events leading to dose interruption

The incidence of TEAEs leading to interruption of dosing of study treatment was generally low (< 20%) in Study B12302 and Study PSMA-617-01. The overall incidences of TEAEs leading to dose interruption was similar across AAA617 treatment arms. The most frequent TEAEs leading to dose interruption in the AAA617 treatment arms of the pooled safety dataset were in the SOC blood and lymphatic system disorders (7.2%), with most frequent PTs anaemia (3.7%) and thrombocytopenia (2.5%). In the ARPI/ARDT arm of Study B12302, the most frequent TEAEs leading to dose interruption were in the

SOC general disorders and administration site conditions (7.8%) with most frequent PTs asthenia (3.4%).

6.10. Post marketing experience

The most recent Periodic Safety Update Report (PSUR) / Periodic Benefit-Risk Evaluation Report (PBRER) for AAA617 covered the period from 23-Sep-2024 to 22-Mar-2025 [Pluvicto PSUR 23Sep2024-22Mar2025].

Approximately 1,806 patients received AAA617 treatment in marketing authorization holder sponsored investigational clinical trials cumulatively since the Development International Birth Date (29-Jan-2017). No new safety concerns related to AAA617 were identified from the long-term follow up in Study PSMA-617-01.

Since the International Birth Date (23-Mar-2022) up until the Data Lock Point (DLP; 22-Mar-2025); 22,933 patients were treated and 88,561 commercial doses of AAA617 were administered in the US, Canada, EU/EEA, and Rest of World (ROW).

A new safety signal of Myeloid Neoplasia including Myelodysplastic Syndrome was identified from post marketing reports and literature on 22-Apr-2025. The safety signal is under evaluation and the findings with conclusion of the evaluation will be presented in the next PSUR (23-Mar-2025 to 22-Mar 2026).

CHMP's comment

It is agreed that based on cumulative data available for post-marketing usage of AAA617 up to 22-Mar-2025, the known safety profile in the approved indication remains unchanged. A new safety signal of Myeloid Neoplasia including Myelodysplastic Syndrome was identified from post marketing reports and literature on 22-Apr-2025. The safety signal is under evaluation and the findings with conclusion of the evaluation will be presented in the next PSUR (23-Mar-2025 to 22-Mar 2026). However, due to increased exposure to radiation from ¹⁷⁷Lu a causal relations appears possible and thus could be expected. Since this signal will impact also the risk profile in the currently applied target population more information is request to allow a preliminary assessment of this risk based on the available data.

No new other safety concerns were identified from the review of the available post marketing experience in the currently approved indication.

Resulting question

A new safety signal of Myeloid Neoplasia including Myelodysplastic Syndrome was identified from post marketing reports, which is proposed to be further addressed in the next PSUR. However, considering the known increased exposure to radiation from ¹⁷⁷Lu, causal relation with the treatment appears probably and could be somewhat expected.

Since this signal will impact also the risk profile in the currently applied target population, more information is need already at present. The MAH is requested to provide more details to allow a preliminary assessment of this risk based on the available data during this procedure. (OC)

6.11. Discussion on clinical safety

In the pivotal study PSMAfore, ¹⁷⁷Lu-PSMA-617 was investigated vs ARPI switch. This comparator is, however, considered nonstandard of care and, therefore, unacceptable. Although relevant, the safety comparison of ¹⁷⁷Lu-PSMA-617 vs ARPI switch in PSMAfore is, therefore, not considered key for the

B/R. Hence, this discussion will focus more on comparing the safety of ^{177}Lu -PSMA-617 in PSMAfore vs the safety of ^{177}Lu -PSMA-617 in VISION, i.e., the known safety profile of Pluvicto ([Pluvicto EPAR](#); [Pluvicto SmPC](#)). It is, however, acknowledged that patients in PSMAfore (post ARPI) were less pretreated than patients in VISION (post ARPI and taxane).

Safety data collection – The [PSMAfore safety analysis](#) for the randomized treatment period is based on the safety set that included all patients who received at least one dose of study treatment (i.e. at least one dose ^{177}Lu -PSMA-617 [n=227] or ARPIs [n=232]), and on the final OS analysis DCO date (01-Jan-2025).

Additionally, safety analyses of all patients that received one dose of ^{177}Lu -PSMA-617 were performed in the Lu-PSMA-617 safety set that included all patients who received at least one dose of ^{177}Lu -PSMA-617, during the randomized part of the protocol or after crossover (n=141).

In PSMAfore, the ^{177}Lu -PSMA-617 dosing regimen was 7.4 GBq once every 6 weeks for 6 cycles.

The [pooled safety data set](#) includes data from the above PSMAfore safety analysis and data from the MAA pivotal study VISION ([Pluvicto EPAR](#)) using the DCO date of 14-Dec-2023 (i.e., the final results from VISION that were provided in procedure II/0022 and were used to update the [Pluvicto SmPC](#) [e.g., section 4.8]).

VISION included a substudy in which 30 additional patients received ^{177}Lu -PSMA-617 outside of the randomization in order to assess pharmacokinetic, dosimetry and ECG. Results from these 30 patients enrolled to ^{177}Lu -PSMA-617+BSC/BSoC in the substudy are reported together with those from the main study VISION in the ^{177}Lu -PSMA-617+BSC/BSoC arm (n=529), adding up to a total of n=559 patients. In VISION, the ^{177}Lu -PSMA-617 dosing regimen was 7.4 GBq once every 6 weeks for *up to* 6 cycles, i.e., after 4 cycles investigators decided whether patients could receive an additional 2 cycles.

In total, the pooled safety data set includes n=927 patients and this is considered a safety database of sufficient size.

Patient exposure – The median number of ^{177}Lu -PSMA-617 doses received in PSMAfore (during randomized part; 6.0) was slightly (numerically) higher than in VISION (5.0). In the pooled safety dataset, the median number of doses received was 6.0.

This is also reflected by the median cumulative dose being (numerically) higher in PSMAfore (42.39 GBq) than in VISION (37.36 GBq).

In contrast, the median relative dose intensity in VISION (102.50%) was (numerically) higher than in PSMAfore (97.61%), but this is due to some patients in VISION withdrawing from/dropping out of the study shortly after their first dose (which leads to a calculated very high relative dose intensity [$\geq 200\%$]).

At the time of the final OS analysis DCO date (01-Jan-2025), the minimum study follow-up was 26.9 months (from randomization to cutoff) and median patient follow-up for OS was 22.75 months (from randomization to last contact date) in the ^{177}Lu -PSMA-617 arm. This length of follow-up is considered sufficient given the intended use of the product.

In comparison, at the time of VISION final analysis the median follow-up duration was 14.2 months ([Pluvicto SmPC](#)).

For completeness, the MAH is requested to complete the (EMA template) table on patient exposure (**Co-Rapp OC**).

Patient disposition – In PSMAfore, 57.7% of patients completed treatment in the ^{177}Lu -PSMA-617 arm, compared to 46.5% in VISION. The most frequent reasons for discontinuation from ^{177}Lu -PSMA-617 in (the randomized part of) PSMAfore was progressive disease 23.8%, while 5.3% of

patients discontinued due to an AE. In VISION, these percentages were 24.0% and 10.2%, respectively. A lower percentage of patients thus discontinued ¹⁷⁷Lu-PSMA-617 treatment due to an AE in PSMAfore compared to in VISION. Since treatment in the ARPI arm was continued until disease progression or unacceptable toxicity, patients in that study arm could not 'complete' treatment.

Demographic and other characteristics of study population – Obviously, patients in PSMAfore (post ARPI) were less pretreated than patients in VISION (post ARPI and taxane).

Overview of AEs – In PSMAfore, the incidence of AEs was close to 100% in both study arms. The incidence of treatment-related AEs was (numerically) higher in the ¹⁷⁷Lu-PSMA-617 arm compared to the ARPI arm. The incidences of Grade ≥3 AEs and SAEs were, however, (numerically) lower in the ¹⁷⁷Lu-PSMA-617 arm compared to the ARPI arm. The incidences of the other categories of AEs were similar in both arms.

There were few fatal SAEs in PSMAfore and none in the ¹⁷⁷Lu-PSMA-617 arm were considered treatment related vs a single patient in the ARPI arm who had a treatment-related fatal SAE (cerebrovascular accident).

The safety profile of ¹⁷⁷Lu-PSMA-617 in PSMAfore was in general similar to the safety profile of ¹⁷⁷Lu-PSMA-617 in VISION. The frequencies of (treatment-related) Grade ≥3 AEs, SAEs and (treatment-related) AEs leading to discontinuation were, however, (numerically) lower in PSMAfore. This could be a reflection of the PSMAfore patient population being less heavily pretreated/earlier-line than the VISION patient population.

Adverse events (AEs) – The most frequent AEs irrespective of causality in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were dry mouth (59.5%), nausea (32.6%), asthenia (32.2%), anaemia (27.3%), fatigue (23.8%), and constipation (22.0%). This is very similar to in VISION and thus the known safety profile of ¹⁷⁷Lu-PSMA-617 ([Pluvicto SmPC](#)).

The most frequent Grade ≥3 AEs irrespective of causality in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were anaemia (6.2%), lymphocyte count decreased (4.0%), blood alkaline phosphatase increased (3.1%), and thrombocytopenia (2.2%). This is also similar to in VISION, although there the incidence of anaemia, thrombocytopenia and lymphopenia was (numerically) higher ([Pluvicto SmPC](#)). This could also be a reflection of the VISION patient population being more heavily pretreated/later-line than the PSMAfore patient population.

Time to resolution of AEs – In PSMAfore, the time to resolution of selected (Grade ≥3) AEs was assessed (PTs: acute kidney injury, anaemia, blood creatinine increased, dry eye, dry mouth, neutropenia, renal failure, thrombocytopenia). This analysis was performed on the subset of patients experiencing at least one TEAE for the PT considered during the on-treatment period, regardless of the relationship to study treatment.

For several AEs this analysis was, however, hampered since in the majority of patients the events had not yet resolved at the DCO date (see below). The median time (range) to resolution was for blood creatinine increased 0.92 (0.3-16.2) months (AE resolved in 9/10 patients) and for acute kidney injury 0.08 (0.0-0.2) months (AE resolved in 4/4 patients).

Treatment-related AEs – The most frequent treatment-related AEs in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were dry mouth (57.7%), nausea (26.4%), asthenia (23.8%), fatigue (18.5%), and anaemia (15.4%). Again, this is very similar to in VISION and thus the known safety profile of ¹⁷⁷Lu-PSMA-617.

The most frequent treatment-related Grade ≥3 AEs in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were anaemia (3.5%) and thrombocytopenia (1.8%). This is also similar to in VISION, although there the incidence of anaemia and thrombocytopenia was (numerically) higher.

Deaths – In the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore, there were 138 (60.8%) deaths, mostly with 'Study indication or disease progression' as the primary reason (112 [49.3%] deaths). Among the other reasons for death (26 [11.5%] deaths) were 7 deaths under the SOC 'Infection and Infestations' (including 2 events of sepsis), 4 deaths under the SOC 'Cardiac disorders', 3 deaths under the SOC 'Nervous system disorders', and 2 deaths due to intestinal ischemia. None of these deaths was considered treatment related.

In the ARPI arm of PSMAfore, there were 155 (66.8%) deaths, mostly with 'Study indication or disease progression' as the primary reason (128 [55.2%] deaths). Among the other reasons for death (27 [11.6%] deaths) were 3 deaths under the SOC 'Infection and Infestations', 3 deaths under the SOC 'Cardiac disorders', and 3 deaths under the SOC 'Nervous system disorders'. There was a single (0.4%) fatal cerebrovascular accident event that was considered treatment-related.

In the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore, there were 4 (1.8%) deaths on treatment with the reason for death being cardiac arrest, intestinal ischemia, COVID-19 pneumonia, and sepsis (all in 1 patient each). None of these on-treatment deaths was considered treatment related.

The proportion of patients who died was (numerically) lower in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore than in VISION, which could be due to the longer duration of follow-up and more advanced disease of the patient population in VISION.

Other SAEs – The incidence of SAEs in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore (20.3%) was (numerically) lower than in VISION (36.5%). This could be a reflection of the PSMAfore patient population being less pretreated/earlier-line than the VISION patient population. The most frequent SAEs in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were anaemia and urinary tract infection (4 [1.8%] patients each), and sepsis (3 [1.3%] patients). Anaemia and urinary tract infection were also the most frequent SAEs in VISION.

In PSMAfore, the incidence of SAEs in the ARPI arm was (32.8%) was (numerically) higher than in the ¹⁷⁷Lu-PSMA-617 arm. The most frequent SAEs in the ARPI arm were acute kidney injury and spinal cord compression (5 [2.2%] patients each), and urinary tract infection, back pain and pain (4 [1.7%] patients each).

The incidence of treatment-related SAEs in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore (4.0%) was also (numerically) lower than in VISION (9.5%).

The most frequent treatment-related SAE in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore was anaemia (3 [1.3%] patients). Anaemia was also the most frequent treatment-related SAE in VISION.

ADRs of special interest – The safety topics of interest (STIs) for ¹⁷⁷Lu-PSMA-617 are: dry mouth, myelosuppression, hepatotoxicity, dry eye, renal toxicity, fractures, QT prolongation, second primary malignancies, intracranial haemorrhage, and radiotoxicity including inadvertent exposure.

No new STIs were identified in analyses of the pooled safety dataset. No new or unexpected safety concern was raised during treatment with ¹⁷⁷Lu-PSMA-617 in PSMAfore.

Dry mouth – The frequency of dry mouth events was even (numerically) higher in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore (60.8%) than in VISION (38.1%), but Grade ≥3 events were very rare (0.9% and 0%, respectively).

The vast majority of these dry mouth events was considered treatment related, i.e., 59.0% and 35.4%, respectively.

In the vast majority of patients in both studies with a dry mouth event, the ¹⁷⁷Lu-PSMA-617 dose was not changed.

At the DCO date, the dry mouth event(s) had not yet resolved in 29.1% of patients in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore, was resolving in 7.9%, and had resolved in 28.6%.

Myelosuppression – The frequency of myelosuppression events was similar in PSMAfore (39.2%) and VISION (47.0%). Grade ≥ 3 events were, however, (numerically) more common in VISION (13.2% vs 23.3%, respectively) in which there were 3 Grade 5 events (2 pancytopenias and 1 bone marrow failure; [Pluvicto EPAR](#)). In PSMAfore, there was one Grade 5 event of bone marrow failure which occurred during the long-term follow-up (LTFU) period (i.e., on Day 283, after the patient had permanently discontinued treatment with ^{177}Lu -PSMA-617 due to thrombocytopenia on Day 216 [after 5 doses]). This Grade 5 event of bone marrow failure in the LTFU period was considered treatment related by the study Sponsor.

The majority of the myelosuppression events was considered treatment related, i.e., 26.9% and 40.3%, respectively.

In the vast majority of patients in both studies with a myelosuppression event, the ^{177}Lu -PSMA-617 dose was not changed.

At the DCO date, the myelosuppression event(s) had not yet resolved in 23.8% of patients in the ^{177}Lu -PSMA-617 arm of PSMAfore, was resolving in 6.6%, and had resolved in 20.3%.

Hepatotoxicity – The frequency of hepatotoxicity events was similar in PSMAfore (12.8%) and VISION (10.0%), but Grade ≥ 3 events were (numerically) more common in PSMAfore (5.3% vs 2.7%, respectively).

In contrast, a (numerically) higher rate of hepatotoxicity events was considered treatment related in VISION, 1.8% vs 3.9%, respectively.

In virtually all patients in both studies with a hepatotoxicity event, the ^{177}Lu -PSMA-617 dose was not changed.

At the DCO date, the hepatotoxicity event(s) had not yet resolved in 6.6% of patients in the ^{177}Lu -PSMA-617 arm of PSMAfore, was resolving in 0.9%, and had resolved in 6.2%.

Dry eye – The frequency of dry eye events was (numerically) higher in the ^{177}Lu -PSMA-617 arm of PSMAfore (6.6%) than in VISION (2.9%), with no Grade ≥ 3 events in either study.

Renal toxicity – The frequency of renal toxicity events was similar in the ^{177}Lu -PSMA-617 arms of PSMAfore (6.2%) and VISION (9.7%), but Grade ≥ 3 events were (numerically) more common in VISION (0.9% vs 3.4%, respectively).

In PSMAfore, half of the renal toxicity events (3.1%) were considered treatment related.

In almost all patients in both studies with a renal toxicity event, the ^{177}Lu -PSMA-617 dose was not changed.

At the DCO date, the renal toxicity event(s) in PSMAfore had resolved in 5.7% of patients in the ^{177}Lu -PSMA-617 arm of PSMAfore, was resolving in 0.4%, and had not yet resolved in 1.3%.

In PSMAfore, safety dosimetry assessments of the kidneys were evaluated in 5 German patients. The mean absorbed dose to the kidneys after a single cycle of treatment was found to be 0.51 ± 0.15 Gy/GBq and the estimated cumulative dose incurred after the full 6 cycles of treatment was 22.5 ± 6.7 Gy. These numbers are considered comparable those from the VISION sub-study reported in the [Pluvicto EPAR](#) and [Pluvicto SmPC](#): 0.43 ± 0.16 mGy/MBq (=Gy/GBq) and 19 ± 7.3 Gy, respectively.

Fractures – Fractures were reported at a similar frequency in the ^{177}Lu -PSMA-617 arm of PSMAfore (4.0%) and VISION (5.7%), with few Grade ≥ 3 events (0.9% and 2.1%, respectively).

QT prolongation – QT prolongation events including Grade ≥ 3 events were reported with a low frequency in PSMAfore (1.8% and 0.4%, respectively) and VISION (2.0% and 1.6%, respectively).

The STI of QT prolongation is comprised of PTs that include cardiac events that may not necessarily be associated with prolonged QT.

In PSMAfore, a Grade 5 event of cardiac arrest was reported in the ^{177}Lu -PSMA-617 arm, plus a

Grade 5 event of cardio-respiratory arrest in a patient who had crossed over to ¹⁷⁷Lu-PSMA-617 treatment. Both events were, however, considered not treatment related.

Second primary malignancies – Second primary malignancy events were reported in PSMAfore and VISION with low incidence (1.8% and 2.3%, respectively), with few Grade ≥ 3 events (0.9% and 1.1%, respectively). In the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore, cases of basal cell carcinoma, adenocarcinoma of the colon, clear cell renal cell carcinoma (RCC) and RCC (1 patient each; 0.4% each) were reported. In the ARPI arm in PSMAfore, three (1.3%) second primary malignancy events were reported, i.e., cases of basal cell carcinoma, (metastatic) leiomyosarcoma, and transitional cell carcinoma. Of all second primary malignancy events, only a single event in VISION (0.2%) was considered treatment related.

In the LTFU period of the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore, a single second primary malignancy event (0.4%) of clear cell RCC was reported.

Intracranial haemorrhage – Intracranial haemorrhage events including Grade ≥ 3 events were reported with a low frequency in PSMAfore (1.3% and 0.4%, respectively) and VISION (1.3% and 0.9%, respectively).

In PSMAfore, a Grade 5 event of subdural haematoma was reported in a patient who had crossed over to ¹⁷⁷Lu-PSMA-617 treatment. This event was, however, considered not treatment related.

Radiotoxicity including inadvertent exposure – There were no events of radiotoxicity reported in PSMAfore.

Discontinuation due to AEs – The incidence of AEs leading to discontinuation in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore (5.3%) was generally low and, moreover, (numerically) lower than in VISION (¹⁷⁷Lu-PSMA-617.6%). This could be a reflection of the PSMAfore patient population being less pretreated/earlier-line than the VISION patient population. In PSMAfore, the incidence of AEs leading to discontinuation in the ARPI arm (5.2%) was very similar to in the ¹⁷⁷Lu-PSMA-617 arm (5.3%).

The most frequent AE leading to discontinuation in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were dry mouth (n=3) and thrombocytopenia (n=3), both ADRs of Pluvicto.

The most frequent AEs leading to discontinuation in the ¹⁷⁷Lu-PSMA-617 treatment arms of the pooled safety dataset were in the SOC blood and lymphatic system disorders, with most frequent PT thrombocytopenia.

AEs leading to dose adjustment – The incidence of AEs leading to dose adjustment in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore (3.5%) was generally low and, again, (numerically) lower than in VISION (5.7%).

The most frequent AE leading to dose adjustment in the ¹⁷⁷Lu-PSMA-617 treatment arm of PSMAfore was dry mouth (n=2).

The most frequent AEs leading to dose adjustment in the ¹⁷⁷Lu-PSMA-617 treatment arms of the pooled safety dataset were in the SOC blood and lymphatic system disorders, with most frequent PT thrombocytopenia.

Safety subgroup analyses – Prespecified safety subgroup analyses were performed for subgroups according to age, race, baseline eGFR level, baseline liver parameters, and region.

Age – The frequency of AEs and Grade ≥ 3 AEs overall, in the SOC of blood and lymphatic system disorders (including anaemia and thrombocytopenia), and in the SOC of gastrointestinal disorders (including dry mouth) was similar for patients in PSMAfore aged <65 years old compared to ≥ 65 years old.

Race – The safety subgroup analysis by race is hampered by the low sample size in race subgroups other than White.

Baseline eGFR level – In both PSMAfore and VISION, patients were required to have a baseline eGFR level ≥ 50 mL/min. Consequently, few patients with moderate renal impairment (eGFR 30 – < 60 mL/min) were enrolled in both studies, i.e., 7.9% and 12.5%, respectively. This hampers the safety analysis in this subgroup.

In both studies, there was an equal distribution of patients across the categories of normal renal function (eGFR ≥ 90 mL/min) and mild renal impairment (eGFR 60 – < 90 mL/min). Across these categories, the frequency of AEs and Grade ≥ 3 AEs overall, thrombocytopenia, and AEs in the SOC of gastrointestinal disorders (including dry mouth) was similar in PSMAfore. Anaemia and Grade ≥ 3 anaemia was (numerically) more common in patients with mild renal impairment (16.8% and 4.2%) than in patients with normal renal function (35.1% and 7.0%) in PSMAfore. While this (numerical) difference was not observed in VISION.

Baseline liver parameters – Very few patients with elevated liver parameters were included in PSMAfore and VISION, which hampers a safety subgroup analysis by baseline liver parameters.

Region – Both PSMAfore and VISION were conducted in Europe and North America (only), which makes a safety subgroup analysis by region less informative.

Post-hoc analyses of safety in asymptomatic/mildly symptomatic subgroup – The safety set of this subgroup in PSMAfore comprised 160/227=70.5% by IRT and 117/227=51.5% by source. The duration and extent of exposure to ^{177}Lu -PSMA-617 in both these subgroups was similar to the overall PSMAfore safety set, e.g., the median number of doses received was also 6.0 in both. The safety profile in both these subgroups, as summarized in the overview of AEs, is similar to the overall/full PSMAfore safety set. This is not surprising, as no clinically relevant difference in ^{177}Lu -PSMA-617 toxicity between the overall PSMAfore safety set and both these subgroups is expected.

Safety in special populations – For completeness, the MAH is requested to complete the (EMA template) table on AEs by age range (**Co-Rapp OC**).

For completeness, the MAH is requested to complete the (EMA template) table on AE by special population (**Co-Rapp OC**).

Safety related to drug-drug interactions and other interactions – There are no known drug interactions with vipivotide tetraxetan and it is unlikely to have any metabolic- or transporter-mediated drug interactions in vivo.

Clinical laboratory evaluations – Haematology – Both in PSMAfore and VISION, the most frequent ($> 90\%$) worst post-baseline haematology abnormalities in the ^{177}Lu -PSMA-617 arm were low lymphocyte and haemoglobin levels. Which is consistent with the AE observations discussed above.

Clinical laboratory evaluations – Clinical chemistry – Both in PSMAfore and VISION, the most frequent worst post-baseline clinical chemistry abnormality was eGFR decreased / creatinine increased (99.6% and 79.6%, respectively), but Grade ≥ 3 events were rare (0.9% and 3.6%, respectively). Incidences of clinical chemistry abnormal increases/decreases in the ^{177}Lu -PSMA-617 arm of PSMAfore were in general (numerically) lower than ^{177}Lu -PSMA-617 arm of VISION, with the exception of alkaline phosphatase increased, eGFR decreased, and sodium increased.

Vital signs – Both in PSMAfore and VISION, notable vital sign values/value changes were typically observed in $< 10\%$ of the patients in the ^{177}Lu -PSMA-617 arm, except for a weight decrease $\geq 10\%$ from baseline, observed in 14.8% and 13.1% of patients, respectively.

ECGs – In PSMAfore, notable changes in ECG were typically observed in <10.0% of patients in the ¹⁷⁷Lu-PSMA-617 arm, and there was a single patient with a QTcF interval (QT interval corrected by Fridericia's formula) increase >60 ms and a single patient with a QT interval >500 ms. This is no reason for concern or further action.

Adverse drug reactions (ADRs) – The selection of ADRs was done as follows. ADR candidates from ¹⁷⁷Lu-PSMA-617, including pre-qualified candidate ADRs and other candidate ADRs, were selected through a process involving medical review of AEs from VISION and PSMAfore and other sources of safety information using principles of causality assessment.

ADRs identified previously from VISION, AEs related to STIs, and designated medical events (DME) were considered as pre-qualified ADR candidates. For new additional ADR candidates from PSMAfore, the criteria for numerical screening were any AE (MedDRA preferred term [PT]) which occurred in ≥5% of patients treated with ¹⁷⁷Lu-PSMA-617 in the safety set of PSMAfore or any AE with a difference of ≥2% between the ¹⁷⁷Lu-PSMA-617 arm and ARPI arm of PSMAfore. Additionally, any AE (MedDRA PT) which occurred in ≥ 5% of patients in the pooled safety set of patients randomized to ¹⁷⁷Lu-PSMA-617 in PSMAfore and VISION were also considered as ADR candidates for evaluation. AEs with reported frequencies of <5% and AEs leading to treatment discontinuation or death in PSMAfore were also considered as new additional ADR candidates from PSMAfore based on clinical assessment of specificity, severity and plausibility. ADR candidates then underwent medical review using the Bradford-Hill criteria to assess the plausibility of a causal association between ¹⁷⁷Lu-PSMA-617 and these ADR candidates, including information available from other sources such as literature. Exposure-adjusted cumulative incidences were also considered during medical review of the ADRs.

This ADR selection process is considered acceptable.

Based on the analysis of the safety data from PSMAfore, no new ADRs were identified. The proposed changes to the ADR table in section 4.8 of the SmPC are mostly editorial, i.e., numerical updates of the number of patients in whom the ADRs occurred. For only two ADRs is a change in frequency category proposed. The proposed changes to the ADR table in section 4.8 of the SmPC are, therefore, considered minor and are acceptable.

Important findings from routine safety signal detection activities – A new safety signal of Myeloid Neoplasia including Myelodysplastic Syndrome was identified from post-marketing reports and literature on 22-Apr-2025. The safety signal is under evaluation and the findings with conclusion of the evaluation will be presented in the next PSUR (23-Mar-2025 to 22-Mar-2026).

Post-marketing surveillance – The most recent Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER) for ¹⁷⁷Lu-PSMA-617 covered the period from 23-Sep-2024 to 22-Mar-2025.

Approximately 1,806 patients received ¹⁷⁷Lu-PSMA-617 treatment in MAH-sponsored investigational clinical trials cumulatively since the Development International Birth Date (29-Jan-2017). Since the International Birth Date (23-Mar-2022) up until the Data Lock Point (DLP; 22-Mar-2025); 22,933 patients were treated and 88,561 commercial doses of ¹⁷⁷Lu-PSMA-617 were administered in the US, Canada, EU/EEA, and Rest of World (ROW).

Impact of safety on subsequent anti-cancer therapies – In PSMAfore, the percentage of patients who received systemic anti-cancer therapy after discontinuation of study drug was 60.7% overall (¹⁷⁷Lu-PSMA-617 arm: 65.0%, ARPI arm: 56.4%, crossover patients: 57.4%). This was most frequently docetaxel, i.e., 51.9% overall (¹⁷⁷Lu-PSMA-617 arm: 55.1%, ARPI arm: 48.7%, crossover

patients: 52.5%), followed by cabazitaxel with 19.2% overall (¹⁷⁷Lu-PSMA-617 arm: 18.9%, ARPI arm: 19.4%, crossover patients: 21.3%).

The impact of ¹⁷⁷Lu-PSMA-617 treatment on, e.g., the exposure and tolerability to docetaxel seems limited, as the median number of number of cycles of docetaxel received was 6.0 in patients in/from the ¹⁷⁷Lu-PSMA-617 arm who received docetaxel as subsequent anti-cancer therapy (i.e., in line with the approved/recommended posology, see, e.g., [Taxotere SmPC](#)).

In the full analysis set, 36.1% of patients overall did not receive any subsequent anti-cancer therapy (¹⁷⁷Lu-PSMA-617 arm: 35.0%, ARPI arm: 37.2%, crossover patients: 39.0%). Reassuringly, the most frequent reason for this was no evidence of disease progression following end of study treatment (i.e., 9.8% overall, ¹⁷⁷Lu-PSMA-617 arm: 12.4%, ARPI arm: 7.3%, crossover patients: 11.3%).

Discontinuation from study was, however, almost as common (i.e., 9.4% overall, ¹⁷⁷Lu-PSMA-617 arm: 8.1%, ARPI arm: 10.7%, crossover patients: 9.2%). Poor performance status as reason for not receiving subsequent anti-cancer therapy was reported in 6.6% overall (¹⁷⁷Lu-PSMA-617 arm: 4.7%, ARPI arm: 8.5%, crossover patients: 7.1%) and toxicity from prior study treatment as reason was very rare (0.4% overall).

Additional expert consultations

Not applicable.

Assessment of paediatric data on clinical safety

Not applicable

6.12. Conclusions on clinical safety

In the pivotal study PSMAfore, ¹⁷⁷Lu-PSMA-617 was investigated vs ARPI switch which is, however, considered a nonstandard-of-care and, therefore, unacceptable comparator. Although relevant, the safety comparison of ¹⁷⁷Lu-PSMA-617 vs ARPI switch in PSMAfore is, therefore, not considered key for the B/R. The focus should be on comparing the safety of ¹⁷⁷Lu-PSMA-617 in PSMAfore vs the safety of ¹⁷⁷Lu-PSMA-617 in VISION (the known safety profile of Pluvicto), while acknowledging that patients in PSMAfore (post ARPI) were less pretreated than patients in VISION (post ARPI and taxane).

The safety profile of ¹⁷⁷Lu-PSMA-617 in PSMAfore was in general similar to the safety profile of ¹⁷⁷Lu-PSMA-617 in VISION (and thus the known safety profile of Pluvicto). The frequencies of (treatment-related) Grade ≥ 3 AEs, SAEs and (treatment-related) AEs leading to discontinuation were, however, (numerically) lower in PSMAfore. There were no treatment-related deaths in PSMAfore.

The most frequent (Grade ≥ 3) AEs both irrespective of causality and treatment related in the ¹⁷⁷Lu-PSMA-617 arm of PSMAfore were in general very similar to in VISION and thus the known safety profile of ¹⁷⁷Lu-PSMA-617. No new ADRs were identified in PSMAfore.

Regarding the safety topics of interest (STIs) for ¹⁷⁷Lu-PSMA-617, no new or unexpected safety concern was raised during treatment with ¹⁷⁷Lu-PSMA-617 in PSMAfore.

The impact of ¹⁷⁷Lu-PSMA-617 treatment in PSMAfore on the patient's ability to receive further anti-cancer therapy seems limited. Then again, given that over half of patients received chemotherapy as subsequent anti-cancer therapy, it could be questioned whether the PSMAfore patient population truly consisted of patients for whom chemotherapy was not (yet) clinically indicated (in line with the proposed indication).

All in all, the safety of ^{177}Lu -PSMA-617 at the approved posology in PSMAfore was in general similar to its known safety profile ([Pluvicto EPAR](#); [Pluvicto SmPC](#)).

6.13. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

6.14. Direct Healthcare Professional Communication

Not applicable

7. Significance of paediatric studies

Not applicable (waiver due to the complete absence of prostate cancer in the paediatric population)

8. Risk management plan

The MAH submitted an updated RMP version 3.0 with this application to support the Type II variation submission proposing for a new indication based on the final OS analysis results of Study AAA617B12302 (hereafter referred to as PSMAfore).

The proposed RMP changes were the following:

Part	Major changes compared to RMP v 2.0
Part I	Proposed draft indication wording added
Part II	None
Module SI	Epidemiology information updated owing to inclusion of new indication
Module SII	None
Module SIII	Updated the clinical trial exposure and exposure tables with pooled safety data from Study CAAA617A12301 (VISION) and Study CAAA617B12302 (PSMAfore).
Module SIV	None
Module SV	Updated post authorization exposure data based on PSUR (23-Mar-2024 to 22-Sep-2024).
Module SVI	None
Module SVII 1.	None
Module SVII 1.2	None
Module SVII 2	None
Module SVII 3.1	Updated tables with pooled safety data from Study CAAA617A12301 (VISION) and Study CAAA617B12302 (PSMAfore).
Module SVII 3.2	None
Module SVIII	None
Part III.2	None
Part III.3	None
Part IV	None
Part V.1	None
Part V.2	None
Part V.3	None
Part VI:I	Updated owing to inclusion of new indication
Part VI:II	None
Part VI:II-IIA	None
Part VI:II-IIB	None

Part VI:II C	None
Part VII	Annex-7 has been updated by deleting Table 7-4 as per the template guidance and also updated the list of references. Annex-8 has been updated to reflect on the changes made to the current RMP.

Part I:

Proposed draft indication wording added:

Treatment of adult patients with PSMA-positive mCRPC who are asymptomatic or mildly symptomatic after having progressed on Androgen Receptor Pathway Inhibitor (ARPI) therapy and for whom chemotherapy is not yet clinically indicated.

PRAC's comment:

The proposed wording reflects the broadening of the indication for Pluvicto to the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI) and for whom chemotherapy is not yet clinically indicated for PLUVICTO, based on interim results from study CAAA617B12302 (PSMAfore).

PSMAfore is a phase III, open-label, multi-center, randomized study comparing 177Lu-PSMA-617 vs. a change of androgen receptor-directed therapy in the treatment of taxane naïve men with progressive metastatic castrate resistant prostate cancer.

Module SI:

Epidemiology information updated owing to inclusion of new indication.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Multivariate analyses showed that high occupational physical activity (AOR 6.7, 95% CI 1.3- 35.1), history of prostatitis (AOR 31.5, 95% CI 9.2-170.5), and old age (over 80 years vs 70 or younger, AOR 299.1, 95% CI 5.3-16985.9) were associated with higher risk of PC (Hosseini et al 2010).

Obesity in general was found to be associated with more aggressive PC with higher risk of biochemical recurrence (HR = 1.20, p = 0.026), risk of CRPC (HR = 2.12, p = 0.026) and risk of mortality (HR 3.38, p = 0.0170) (Vidal et al 2017). Another study showed similar results where high BMI was associated with a trend for greater risk of progression to CRPC (HR: 3.36, 95% CI: 0.96-11.71, p=0.063), risk of developing metastases (HR: 3.58, 95% CI: 0.77-16.65, p=0.027) and a trend toward worse PCSM (HR: 8.21 95% CI: 0.97-69.72, p=0.119) (Keto et al 2012).

In Moldaver et al (2023), demographic characteristics were only reported by type of 1L treatment for mCRPC. The mean age (standard deviation, SD) at mCRPC diagnosis was 74 years (8) for patients who received 1L abiraterone and 73 years (8) for patients who received 1L enzalutamide; the median age (interquartile range, IQR) at mCRPC diagnosis was 73 years (67-80) and 73 years (67-79), respectively.

PRAC's comment:

Scant data is available for the new indication. Moldaver et al (2023) reported limited evidence of the natural history of the indicated condition. Median OS was reported for the aggregated group of mCRPC patients receiving either abiraterone or enzalutamide in the 1L setting for mCRPC - 13.0 months, 95% confidence interval, CI: 11.6-14.5 months. (Median OS for 2L and 3L treatment for mCRPC were not

reported by complete treatment patterns, i.e., the median OS of mCRPC patients receiving a switch in ARPI therapy from 1L to 2L mCRPC treatment and who did not receive chemotherapy in the mCRPC setting could not be determined from the literature). Moldaver et al (2023) reported comorbidities only by type of 1L treatment for mCRPC. The mean (SD) Charlson Comorbidity Index (CCI) at mCRPC diagnosis was 0.4 (0.9) [median (IQR): 0 (0-1)] for patients who received 1L abiraterone for the treatment of mCRPC and 0.5 (0.9) [median (IQR): 0 (0-1)] for patients who received 1L enzalutamide for the treatment of mCRPC. Among the 498 patients who received 1L abiraterone for the treatment of mCRPC and with known Charlson category, 370 patients (74.3%) were classified as Charlson category 0, 82 patients (16.5%) were classified as Charlson category 1, and 46 patients (9.2%) were classified as Charlson categories 2+. For the 317 patients who received 1L enzalutamide for the treatment of mCRPC and with known Charlson category, 210 patients (66.2%) were classified as Charlson category 0, 61 patients (19.2%) were classified as Charlson category 1, and 46 patients (14.5%) were classified as Charlson category 2+.

Module SIII:

Updated the clinical trial exposure and exposure tables with pooled safety data from Study CAAA617A12301 (VISION) and Study CAAA617B12302 (PSMAfore).

This RMP version presents the pooled safety data from two studies:

1) the Phase III studies CAAA617A12301 (VISION): An international, prospective, open-label, multicentre, randomized Phase 3 study of ¹⁷⁷Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive mCRPC, and

2) CAAA617B12302 (PSMAfore): An open-label, multicentre, randomized Phase 3 study comparing ¹⁷⁷Lu-PSMA-617 vs. a change of androgen receptor-directed therapy (ARDT) in the treatment of taxane naïve men with progressive mCRPC.

The pooled safety data are based on 756 patients who were randomized to receive at least one dose of [¹⁷⁷Lu]Lu-PSMA- 617 from the VISION and PSMAfore studies.

PRAC's comment:

Updated clinical trial exposure with pooled safety data have been included in the RMP. This is acceptable.

The following sections of the RMP have been updated in line with the sections above:

Module SIII, Module SV, Module SVII 3.1, Part VI:I and Part VII.

These are acceptable modifications.

Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

9. Benefit-Risk Balance

9.1. Therapeutic Context

Pluvicto is a Radioligand therapy product which contains lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu]Lu-PSMA-617 / AAA617) and is currently **approved for the indication:**

in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition is indicated for the treatment of adult patients with progressive prostate specific membrane antigen (PSMA)-positive metastatic castration resistant prostate cancer (mCRPC) who have been treated with AR pathway inhibition and taxane-based chemotherapy (see section 5.1).

With this procedure the MAH applies for the **extension of indication**

for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) therapy and for whom chemotherapy is not yet clinically indicated (see section 5.1).

Application is based on one pivotal trial, CAAA617B12302 (PSMAfore-Trial)

Study CAAA617B12302 is a randomised (1:1), controlled, open-label phase 3 study comparing Pluvicto versus 'change in ARPI treatment' (i.e. abiraterone or enzalutamide per physician's choice) in 468 patients with PSMA-positive mCRPC having progressed once on an ARPI (abiraterone, enzalutamide, darolutamide or apalutamide). Patients maintained castrate levels of serum/plasma testosterone by either medical castration or prior orchiectomy. Patients randomised to the 'change in ARPI' arm were allowed to cross over to receive Pluvicto upon radiographic disease progression (i.e. before treatment with taxane-based chemotherapy). The primary endpoint was rPFS (as determined by BICR per PCWG3 criteria), key secondary endpoint was OS. Randomisation was stratified by 'setting of prior ARPI use' (CRPC versus HSPC) and by 'symptomatology' (asymptomatic or mildly symptomatic versus symptomatic). The study was initiated in June 2021.

9.1.1. Disease or condition

Prostate cancer is the third leading cause of cancer-related deaths among men in Europe (Malvezzi et al 2023, Siegel et al 2024). In Europe, 473,011 new cases and 115,182 deaths were estimated for 2022 (International Agency for Research on Cancer 2022).

Most patients with prostate cancer present with localised disease and undergo initial surgical and/or radiation therapy, with concomitant or subsequent use of androgen deprivation therapy (ADT) and other treatments. Prostate cancer patients who develop metastasis after treatment of localised disease, and patients who present with de novo metastatic disease inevitably develop castration resistance, resulting in transition from metastatic hormone sensitive prostate cancer (mHSPC) to mCRPC. ARPI/ARDTs can be highly effective in eliciting a therapeutic response.

However, the majority of mCRPC patients suffer morbidity from their disease including bone metastases and symptomatic (e.g. pain) and/or serious skeletal events (e.g. fractures) that significantly affect quality of life and shorten median overall survival (OS), which remains ≤ 2 years (Bubendorf et al 2000; Marques et al 2010; McKay et al 2017; Liu et al 2020; Freedland et al 2023; Schaeffer et al 2023).

Since PSMA is expressed in >80% of men with prostate cancer, PSMA-targeted RLT offers the possibility of treating the cancer lesions in a specific and tumour-selective manner by exploiting cell surface receptors that are highly expressed on malignant prostate cancer cells as compared to normal cells.

Based on the phase III Study PSMA-617-01 (also known as VISION), AAA617 (Pluvicto) was approved for adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI/ARDT and taxane-based chemotherapy.

Advancing this therapy to earlier lines of treatment is now applied for patients with PSMA-positive mCRPC patients who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) therapy and for whom chemotherapy is not yet clinically indicated

9.1.2. Available therapies and unmet medical need

For the assessment of this application, it is important to consider the sequences of treatment lines in mCRPC as described in the scientific European EAU guideline for prostate cancer (updated March 2025):

The majority of mCRPC patients present with bone metastases and may develop symptomatic (e.g. pain) and/or severe (e.g. fractures) serious skeletal events that significantly affect quality of life and shorten median overall survival (OS), which remains ≤ 2 years.

Patients with metastatic disease, presenting initially or after localized treatment, are managed according to the EAU guideline with ARDT as first line treatment.

ARDT, androgen deprivation therapy (ADT), and androgen receptor (AR) pathway inhibitors (ARPI) can be highly effective in eliciting a prostate specific antigen (PSA) response. However, the development of resistance to androgen suppression is inevitable, resulting in transition to metastatic castration-resistant prostate cancer and disease progression.

Thus, the EAU guideline recommends after progression on ADT/ARDT/ARPI treatment for the second line the use of chemotherapy with docetaxel and subsequent cabazitaxel in the treatment sequence. The guideline emphasizes that chemotherapy should be applied early enough when the patient is still fit for chemotherapy and not be delayed. This is supported by high-level evidence showing an increase in PFS and OS from chemotherapy in the second line mCRPC.

Moreover, the guideline clarified that a sequencing of androgen receptor targeted agents at this stage should be avoided.

Treatment beyond the second line ("patients with mCRPC and progression following docetaxel chemotherapy") is more complicated and heterogeneous due to the issue that the EAU guideline recommends strongly that "the choice of treatment on the performance status (PS), symptoms, co-morbidities, location and extent of disease, genomic profile, patient preference, and on previous treatment for hormone-sensitive metastatic PCa (mHSPC) (alphabetical order: abiraterone, cabazitaxel, docetaxel, enzalutamide, 177lutetium-PSMA-617-radioligand therapy, radium-223, sipuleucel-T, and for patients with DNA homologous recombination repair (HRR) alterations olaparib, olaparib/abiraterone, niraparib/abiraterone, rucaparib, talazoparib/enzalutamide)."

Thus, the use of Pluvicto (177Lu-PSMA-617) is currently recommended in the guideline in the third line for pre-treated mCRPC patients with one or more metastatic lesions, highly expressing PSMA (exceeding the uptake in the liver) on the diagnostic radiolabelled PSMA PET/CT scan.

Now the MAH applies for the treatment of a less advanced population of mCRPC in an earlier treatment line, which is currently not established in the sequencing of treatment. The intended target population is mainly characterised by progression after first line ADT/ARDT/ARPI therapy and before any second-line taxane chemotherapy.

Since almost all patients with mCRPC will progress after first-line ARDT, it is likely that nearly all of them would receive AAA617 in the next step as second line treatment. Docetaxel-chemotherapy, will become delayed and third line treatment, although it remains unknown whether chemotherapy after AAA617 is still as beneficial as currently documented. This proposal is not in accordance with the current guideline recommendation.

The applicant justifies this decision with the argument that “to provide *the mCRPC population with a high medical need an effective and well tolerated alternative option for patients who desire to defer or completely avoid chemotherapy after initial progression on ARPI.*

The intent of PSMAfore was to demonstrate that AAA617 provides an alternative treatment with mechanistic switch and meaningfully improved outcomes for mCRPC patients after first progression on ARPI. Other trials in chemotherapy-naïve mCRPC have likewise used ARPI switch included as comparator arm (CONTACT-02, TRITON3, and SPLASH), in recognition of this particular subpopulation with unmet need (de Bono et al 2020, Fizazi et al 2023, Agarwal et al 2024, Hansen et al 2025).

Although the intention to develop treatment alternatives is endorsed, it remains incomprehensible that the MAH has not previously discussed the approach and the trial design with CHMP considering the significant change in treatment lines for mCRPC applied. Particularly in a situation like here, in which the intended treatment line is not established and additionally contradicts the current EU-treatment standards, a Scientific advice would have been indicated.

9.1.3. Main clinical studies

9.2. Favourable effects

In Study B12302, the primary efficacy endpoint was met showing a statistically significant rPFS benefit (HR=0.41; 95% CI: 0.29, 0.56; $p<0.0001$) for PSMA-positive mCRPC patients treated with AAA617 compared to ARPI/ARDT change after being treated with an ARPI/ARDT (DCO 02-Oct-2022).

At the final OS analysis being based on 299 events (DCO 01-Jan-2025), the study did not meet its key secondary endpoint of OS with a HR of 0.91 (95% CI: 0.72, 1.14; $p<0.2$), estimated median OS was 24.48 months (95% CI: 19.55, 28.94) and 23.13 months (95% CI: 19.61, 25.53), respectively.

9.3. Uncertainties and limitations about favourable effects

The control arm treatment in PSMAfore is inadequate, as the [EAU](#) and [ESMO guidelines](#) advise against ARPI switch since there is evidence suggesting cross-resistance between abiraterone and enzalutamide. Moreover, a second AR inhibitor has shown only modest activity.

The appropriate comparator in the post-ARPI mCRPC setting would be docetaxel. Importantly, the randomised phase II CCTG PR.21 study (NCT04663997) recently conducted in this disease setting showed that there was no indication of an rPFS benefit of ^{177}Lu PSMA 617 versus docetaxel (median rPFS 8.6 vs 10.7 months, respectively), while there was a possible OS detriment (median OS 14.3 vs 18.2 months, respectively) ([Chi et al. ESMO 2025 abstract](#)). **The allowance of crossover severely limits the ability to draw a conclusion on OS.** Importantly, ^{177}Lu -PSMA-617 is not an

approved/established treatment option in taxane-naïve patients. OS analyses adjusting for crossover are not considered to be reliable due to a possible data-driven methodology and uncertainty whether model assumptions are met.

Any move to introduce an earlier treatment line also requires information about the impact on outcomes of subsequent treatment lines. At present, it remains unknown whether the efficacy of docetaxel and other chemotherapies after prior administration of Lu-PSMA-617 is comparable to that documented under the current recommendation (third-line treatment with Lu-PSMA-617 as shown in VISION).

Serious TEAEs in PSMAfore occurred more often in the Control arm compared with AAA617 arm (PSMA: 20.3% versus ARDT 32.8%; Grade >3 events 18.1% versus 30.2). This unusual finding may confirm insufficient treatment in the control arm due to delay in chemotherapy. In particular, since safety outcome of chemotherapy after AAA617 remains unknown, while chemotherapy before AAA617 has been proven to prolong PFS and OS.

The intended target population is not sufficiently characterised and not in line with the studied population. Considering that the EAU guideline recommends chemotherapy as the best treatment option after first-line progression for all mCRPC patients, it remains unknown how patients “*for whom chemotherapy is not yet clinically indicated*” can be appropriately identified and differentiated from those requiring immediate chemotherapy. Moreover, this criteria was not reflected in the inclusion/exclusion criteria of the PSMAfore trial. Similarly, no eligibility criteria were formulated related to the proposed restriction of the target population to “*asymptomatic or mildly symptomatic patients*”. Of note, the risk of over-broad and premature treatment with Lu-PSMA-617 in the proposed indication needs to be considered.

9.4. Unfavourable effects

The analysis confirmed the known safety profile and good tolerability of AAA617 in mCRPC patients from the previous VISION Study PSMA-617-01 and post-marketing experience.

In Study B12302, patients in the AAA617 arm had lower rates of Grade ≥ 3 AEs, SAEs, TEAEs requiring dose adjustment, and TEAEs leading to interruption compared to the ARPI/ARDT treatment arm. The incidences of fatal SAEs and TEAEs leading to discontinuation were comparable between the two treatment arms.

The safety of AAA617 was also evaluated across subgroups of age, race, geographical region, baseline eGFR and baseline liver parameters. No unexpected differences were observed in any of the subgroups. The evaluation also revealed no new ADR for AAA617.

Regarding safety topics of interest (myelosuppression, renal toxicity, dry mouth, dry eye, fractures, intracranial haemorrhage, second primary malignancies, QT prolongation, and hepatotoxicity), no new safety concerns were identified and the risk profile of AAA617 remains unchanged.

The assessment of all deaths indicates no potential harm or increased toxicity in the AAA617 arm as compared to the ARPI/ARDT arm.

Data collected from patients in the LTFU, i.e. after end-of-treatment in Study B12302 and Study PSMA-617-01, did not reveal new safety concerns or new serious risks, potential serious signals of second primary malignancies, or other serious long-term outcomes in patients receiving AAA617, with exception of myelodysplasia probably leading to leukaemia or aplasia (known risk for all radioligand therapeutics).

The nature and severity of AEs in LTFU were similar to those TEAEs observed during randomised treatment.

9.5. Uncertainties and limitations about unfavourable effects

In the pivotal study PSMAfore, 177Lu PSMA 617 was investigated vs ARPI switch which is, however, considered a nonstandard of care and, therefore, unacceptable comparator. Although relevant, the safety comparison of 177Lu PSMA 617 vs ARPI switch in PSMAfore is, therefore, not considered key for the B/R. The focus should be on comparing the safety of 177Lu PSMA 617 in PSMAfore vs the safety of 177Lu PSMA 617 in VISION (the known safety profile of Pluvicto), while acknowledging that patients in PSMAfore (post ARPI) were less pretreated than patients in VISION (post ARPI and taxane).

It remains uncertain whether Pluvicto maintained the patient's ability to receive further antineoplastic therapy with the same benefits and risk as currently established according to the existing guidelines.

It is unknown whether the currently approved treatment with Pluvicto after taxane chemotherapy in the third line will be still beneficial as currently approved.

The long-term follow-up period in Studies B12302 and PSMA-617-01 allowed for collecting additional data on outcomes and safety beyond the on-treatment period and further informing the safety profile of AAA617. However, due to the differences in AE reporting methodologies, study treatment and characteristics of the patient populations in the pooled safety dataset, limited comparisons can be made across both studies.

STIs beyond the safety period were recorded for selected AEs but only for patients who received AAA617 treatment, therefore a comparison to the ARPI/ARDT arm is not possible. However, it is acknowledged that many of these AEs occurred with subsequent treatments including chemotherapy and thus may not reflect only toxicities from AAA617.

Finally, the open-label design may have an influence on the reporting of AEs. While blinding was not feasible considering the differences in formulation and treatment schedule between the treatment arms, the schedule of safety follow-up assessments were identical for both treatment arms.

9.6. Effects Table

Effects Table for Pluvicto in the indication "*treatment of (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) therapy and for whom chemotherapy is not yet clinically indicated*"

Effect	Short description	Unit	Treatment [177Lu]Lu-PSMA-617 (95% CI)	Control ARDT (95% CI)	Uncertainties / Strength of evidence/ HR (95% CI)	DCO
Favourable Effects						
Primary endpoint Radiographic progression-free survival	rPFS	Median time in months (95% CI)	9.30 (6.77, NE)	5.55 (4.04, 5.95)	rPFS HR: 0.41 (0.29, 0.56) 3.75 months	02-Oct-2022
Key secondary endpoint Overall survival	OS	Median time in months (95% CI)	24.48 (19.55, 28.94)	23.13 (19.61, 25.53)	OS HR: 0.91 (0.72, 1.14)	01-Jan-2025

Effect	Short description	Unit	Treatment [177Lu]Lu-PSMA-617 (95% CI)	Control ARDT (95% CI)	Uncertainties / Strength of evidence/ HR (95% CI)	DCO
Unfavourable Effects						
AEs (Treatment-related AEs)	Incidence in the PSMAfore target population	%	98.7 (89.4)	98.3 (63.8)	Similar event rates	01-Jan-2025
≥Grade 3 AEs (Treatment-related ≥Grade 3 AEs)	Incidence in the PSMAfore target population	%	35.2 (13.7)	49.1 (12.1)	More total >Grade 3 events in ARPI/ARDT arm	01-Jan-2025
SAEs (Treatment-related SAEs)	Incidence in the PSMAfore target population	%	20.3 (4.0)	32.8 (2.6)	Risk difference in favour for AAA617: 12.5%	01-Jan-2025
Deaths due to AEs (Treatment-related deaths due AEs)	Incidence in the PSMAfore target population	%	1.8 (0)	2.2 (0)	Similar Risk between the arms	01-Jan-2025
Adverse events leading to discontinuation (Treatment-related AEs leading to discontinuation)	Incidence in the PSMAfore target population	%	5.3 (4.0)	5.0 (2.6)	Similar Risk between the arms	01-Jan-2025
Myelosuppression	Incidence in the PSMAfore target population	%	39.2	23.7	Risk difference not in favour for AAA617: +15.5 (6.39,23.88)	01-Jan-2025
Fractures	Incidence in the PSMAfore target population	%	4	8.6	Risk difference in favour for AAA617-4.66 (-9.52, -012)	01-Jan-2025
Hepatotoxicity	Incidence in the PSMAfore target population	%	12.8	13.8	Risk difference in favour for AAA617 -1.02 (-7,46, 2.88)	01-Jan-2025
Renal toxicity	Incidence in the PSMAfore target population	%	6.2	8.2	Risk difference in favour for AAA617 -2.02 (-7.02, 2.88)	01-Jan-2025

9.6.1. Importance of favourable and unfavourable effects

Based on the results from the pivotal study B12302 (PSMAfore), the MAH intends to establish a new treatment-line between the current first and second line (or in fact: a new second line treatment instead of taxane chemotherapy).

In the pivotal study, treatment with ¹⁷⁷Lu-PSMA-617 showed an improvement in rPFS compared to a switch in ARPI in mCRPC patients who have progressed on one prior second-generation ARPI. The key secondary endpoint OS, however, failed to reach statistical significance in the final analysis in which OS data were mature. Some secondary endpoints (TTSSE, TTSTP, PFS) support the primary endpoint, while others are in line with the lack of OS benefit (PFS2, TTCT).

The improvement in rPFS is of unclear clinical relevance, as an ARPI switch is considered to be an inadequate and ineffective control treatment, as noted in relevant guidelines. This was also noted in scientific advice. The appropriate comparator in the post-ARPI mCRPC setting is considered to be docetaxel ([Chi et al. ESMO 2025 abstract](#)).

¹⁷⁷Lu-PSMA-617 treatment in this setting does not result in clinical benefit, as shown by the OS analysis. Importantly, OS has been considered the relevant endpoint for approval in CRPC as other treatments in this setting have shown survival advantage. Further, rPFS has not been established as surrogate endpoint for OS ([Gharzai et al. NEJM Evid. 2023](#)) in CRPC. Another major drawback of the study design is the allowance of crossover to ¹⁷⁷Lu-PSMA-617. Of note, ¹⁷⁷Lu-PSMA-617 treatment is not approved in a taxane-naïve mCRPC setting, thus the study is not representative of treatment available to patients. OS analyses adjusting for cross-over have inconsistent results and are not considered to be reliable due to a possible data-driven methodology and uncertainty whether model assumptions are met. Overall, the rPFS improvement is of unclear clinical relevance and benefit in terms of OS for ¹⁷⁷Lu-PSMA-617 treatment has not been established (**MO**).

The safety of ¹⁷⁷Lu-PSMA-617 at the approved posology in PSMAfore was in general similar to its known safety profile ([Pluvicto EPAR](#); [Pluvicto SmPC](#)). The frequencies of (treatment-related) Grade ≥3 AEs, SAEs and (treatment-related) AEs leading to discontinuation were, however, (numerically) lower in PSMAfore. No new or unexpected safety concern was raised during treatment with ¹⁷⁷Lu-PSMA-617 in PSMAfore and no new ADRs were identified.

The following important remarks are, however, made.

The impact of ¹⁷⁷Lu-PSMA-617 treatment in PSMAfore on the patient's ability to receive further anti-cancer therapy seems limited. Then again, given that over half of patients received chemotherapy as subsequent anti-cancer therapy, it could be questioned whether the PSMAfore patient population truly consisted of patients for whom chemotherapy was not (yet) clinically indicated (in line with the proposed indication).

Importantly, the earlier use of ¹⁷⁷Lu-PSMA-617 (i.e. without a documented OS benefit) would change the recommended treatment sequence in mCRPC. It remains uncertain whether this influences the B/R of subsequent treatment lines.

At the time of MAA, the safety profile of ¹⁷⁷Lu-PSMA-617 – although non-negligible – was outweighed by the compelling efficacy outcome in VISION and the B/R was, therefore, considered positive ([Pluvicto EPAR](#)). The compelling efficacy outcome in VISION was a statistically significant and clinically relevant improvement in OS compared to the BSC/BSoC comparator which was (both at SA and at the time of MAA) considered acceptable since no clear evidence-based treatment recommendations could be given in the applied-for mCRPC setting post ARPI and taxane.

This scenario is, however, not applicable for the current application, as the ARPI switch comparator in PSMAfore is considered nonstandard of care and, therefore, unacceptable. Moreover, no (statistically significant) improvement in OS was demonstrated in PSMAfore. This prevents concluding on a positive B/R.

Regarding the wording of the indication, the following remarks are made.

The term "*who are asymptomatic or mildly symptomatic*" is not supported. Patients were allowed to be included into the study regardless of symptoms and this wording is a post-hoc subgroup selection in which 49% of the study patients are excluded. This subgroup merely seems an attempt to make the inferior comparator more acceptable, mirroring the wording used for the approved agents used as comparator in the study, i.e., [abiraterone](#) or [enzalutamide](#) which both include the wording "*who are asymptomatic or mildly symptomatic after failure of ARDT in whom chemotherapy is not yet clinically indicated*". Importantly though, these approved indications concern an earlier mCRPC treatment line,

i.e., following ADT only. Thus, the wording of the indication does not correspond to the PSMAfore eligibility criteria and is, therefore, no adequate reflection of the studied patient population. Further, all patients in the pivotal study PSMAfore were required to have a castrate level of serum/plasma testosterone and to be (taxane) chemotherapy-naïve. The wording "for whom chemotherapy is not yet clinically indicated" was not among the eligibility criteria. The MAH is, therefore, requested to specify this in the indication wording. (**MO**).

9.1. Benefit-risk assessment and discussion

9.1.1. Balance of benefits and risks

While in PSMAfore a statistically significant prolongation in rPFS was observed, ¹⁷⁷Lu-PSMA-617 treatment did not prolong survival in mCRPC patients who have progressed on one ARPI compared to an ARPI switch. As the control arm treatment is inadequate/ineffective the rPFS effect is considered to be of unknown clinical relevance. This does not outweigh the non-negligible safety profile of ¹⁷⁷Lu-PSMA-617. Moreover, the wording of the indication is not supported.

The B/R for Pluvicto is, therefore, considered **negative**.

9.1.2. Additional considerations on the benefit-risk balance

The input of a SAG oncology is not warranted. The clinical guidelines are sufficiently clear in their (strong) recommendations for the treatment of patients with mCRPC, to: i) avoid sequencing of androgen receptor targeted agents, i.e., avoid ARPI switch; and ii) offer (docetaxel) chemotherapy to patients previously treated with an ARPI.

9.2. Conclusions

The overall B/R of Pluvicto in the applied new indication "for the treatment of (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after having progressed on androgen receptor pathway inhibitor (ARPI/ARDT) therapy and for whom chemotherapy is not yet clinically indicated" is **negative**.

10. References

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