13 October 2022
EMA/871459/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pluvicto

International non-proprietary name: lutetium (177lu) vipivotide tetraxetan

Procedure No. EMEA/H/C/005483/0000

Note

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

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List of abbreviations

AAA	Advanced Accelerator Applications
AE	Adverse event
ALP	Alkaline phosphatase
APCCC	Advanced Prostate Cancer Consensus Conference
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
AUCinf	Area under the curve extrapolated to infinity
BCRP	Breast cancer resistance protein
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Products)
BICR	Blinded independent central review
BPI-SF	Brief Pain Inventory – Short Form
BSC	Best supportive care
BSoC	Best standard of care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CYP	Cytochrome
DCR	Disease control rate
DKFZ	Deutsches Krebsforschungszentrum (German Cancer Research Center)
DoR	Duration of response
DOTA	Dodecane tetraacetic acid
DTPA	Diethyl enetriamine penta acetic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESI	Electrospray ionization
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FAS	Full Analysis Set
FDA	Food and Drug Administration
GBq	Gigabecquerel
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH	International Council for Harmonization
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	Independent Data Monitoring Committee
IR	Infrared

IV	Intravenous
LC MS	Liquid chromatography mass spectrometry
LDH	Lactate dehydrogenase
MAA	Marketing Authorization Application
MATE1/MATE 2	Multidrug and toxin extrusion protein 1/2
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
NAAD	Novel androgen axis drug (for example abiraterone or enzalutamide)
NCCN	Nation Comprehensive Cancer Network
NDA	New drug application
NMR	Nuclear Magnetic Resonance
OAT1/OAT3	Organic anion transporter 1/3
OOCT2	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PC	Prostate cancer
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	Progressive disease
PDE	Permitted Daily Exposure
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PR	Partial response
PROs	Patient reported outcomes
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
QoL	Quality of life
RCP	Radiochemical purity
RECIST	Response Evaluation Criteria in Solid Tumors
RH	Relative Humidity
RLT	Radioligand therapy
RP	Reverse Phase
rPFS	Radiographic progression-free survival
SAE	Serious adverse event
SD	Stable disease
SSE	Symptomatic skeletal event
TEAE	Treatment-emergent adverse event
TLC	Thin layer chromatography
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V	Visible
WoC	Withdrawal of consent

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 30 September 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pluvicto, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 October 2019.

The applicant applied 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 have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0127/2019 on the granting of a product-specific waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

The applicant requested the active substance lutetium (^{177}Lu) vipivotide tetraxetan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 April 2019	EMEA/H/SA/4078/1/2019/III	Martin Mengel, Joao Manuel Lopes de Oliveira

The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the proposed starting materials, specifications for the control of the drug product, and the stability program to support a retest date of PSMA-617 drug substance precursor and shelf-life of ^{177}Lu-PSMA-617 drug product.
- Sufficiency of the proposed non-clinical program to support a MAA.
- Acceptability of the overall clinical development plan, including the design of the pivotal phase 3 study (VISION) to support a MAA.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	30 September 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 May 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	4 July 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022

The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 September 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pluvicto on	13 October 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	13 October 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The initially applied indication for lutetium (^{177}Lu) vipivotide tetraxetan was for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

The target population of PSMA positive mCRPC who have been treated with androgen receptor (AR) pathway inhibition and taxane based chemotherapy is a late line advance cancer population (third line). It is agreed that there are limited options following progression on taxane-based chemotherapy.

2.1.2. Epidemiology

Prostate cancer is globally the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths in 2020 worldwide (Sung et al 2021). It is the second leading cause of cancer-related death among men in the USA, and the third leading cause in Europe (Malvezzi et al 2019, Siegel et al 2020). In the USA, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020), and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths (International Agency for Research on Cancer 2020). The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016).

2.1.3. Biologic features

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

Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, androgen-independent prostate cancer (Wright et al 1995, Silver et al 1997, Bostwick et al 1998, Murphy et al 1998, Sweat et al 1998, Ross et al 2003, Chang 2004, Queisser et al 2015).

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumour-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA leads to internalization through endocytosis, and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003, Benešová et al 2015). This functional feature of PSMA allows for the development of low-molecular weight targeted radiopharmaceuticals with favourable pharmacokinetic and tumour penetration properties, rather than being restricted to antibody-based targeting strategies (Haberkorn et al 2016).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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

Approximately 90% of patients with mCRPC develop bone metastases (Kirby et al 2011), 49% of whom will develop a skeletal-related event within 2 years (Saad et al 2004). Common presentations include bone pain, bone marrow failure, fatigue, or complications such as fractures and spinal cord compression. These presentations typically require radiation or bone surgery, which can significantly impair physical, emotional, and functional well-being (Weinfurt et al 2005).

2.1.5. Management

The current standard of care in metastatic prostate cancer (mPC) is based on chemotherapy, androgen deprivation by different mechanisms of action on the hypothalamic-pituitary-gonadal axis, and adrenal-androgen receptor signaling. Standard ADT and NAADs (i.e. abiraterone acetate or enzalutamide) are commonly well tolerated and can stabilize metastatic castration-sensitive PCs (mCSPC) for many years. However, most patients eventually progress to mCRPC, which remains challenging to treat.

Several agents have been approved for the treatment of mCRPC. NCCN, ASCO, ESMO, and APCCC guidelines provide some consensus and guidance for their use, but there is no proper sequence for delivery of these agents in patients with mCRPC. Regardless, none of these therapies has been proven to prolong survival after NAAD (novel androgen axis drug) therapies.

Taxane-based chemotherapies and androgen axis inhibitors are the most commonly used agents for patients with mCRPC (Tannock et al 2004, de Bono et al 2010, de Bono et al 2011, Scher et al 2012), and only one study (the CARD study) has demonstrated efficacy after progression has occurred following treatment with these agents (Gillessen et al 2020). In the CARD study, cabazitaxel was more effective than switching from abiraterone to enzalutamide, or vice-versa, in both prolonging imaging-based progression-free survival and overall survival of patients with progression after docetaxel and either abiraterone or enzalutamide (de Wit et al, 2019). Other treatment options in this population include bone-directed radiotherapy with 223radium for those with symptomatic bone dominant disease, immunotherapy with sipuleucel-T, and poly ADPribose polymerase (PARP) inhibitors in those with specified HRR defects (Kantoff et al 2010, Parker et al 2013, Abida et al 2020, Anscher et al 2020, de Bono et al 2020, Hussain et al 2020).

In clinical practice, NAADs are often used in the first-line mCRPC setting. Sipuleucel-T is most commonly used in mildly asymptomatic small-volume disease, while 223Ra dichloride is used to treat patients with bone-only disease. Taxane-based chemotherapy (i.e. docetaxel and cabazitaxel) is used after abiraterone acetate or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly (Flaig et al 2016), and cabazitaxel was specifically designed for antitumor activity in docetaxel-resistant patients (de Wit et al 2019). Because both agents have a typical chemotherapy side-effect profile (including bone marrow suppression), they are often not considered due to multiple comorbidities, poor hematological reserve, or patient refusal (Zielinski et al 2014). When the approved second-line treatments (e.g. abiraterone acetate or enzalutamide) are used in the third line setting, they do not retain the same levels of activity as when used in second line.

NAADs in patients previously exposed to a taxane and either abiraterone acetate or enzalutamide produce only modest activity in terms of PSA decline, and PFS and OS benefit (Loriot et al 2013, Noonan et al 2013, Azad et al 2015, Brasso et al 2015, Cheng et al 2015).

As NAADs have been used in earlier lines of therapy, the use of a second NAAD following docetaxel has resulted in diminished efficacy, likely due to cross resistance. In summary, although the therapeutic landscape of mCRPC has broadened over the last decade, deaths due to mCRPC are still rising in these patients, many of whom are frail and elderly.

There are limited options available to patients who fail taxane-based chemotherapy or for whom taxane-based chemotherapy is contraindicated or not appropriate, particularly if alternative agents currently approved in this setting (NAADs) have been used earlier in the disease.

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

Targeted radioligand therapy (RLT) offers the possibility to treat prostate cancer lesions in a specific and tumor-selective manner by exploiting cell surface proteins mainly expressed on malignant cells. The prostate-specific membrane antigen (PSMA) is a promising RLT target because it is highly expressed in PC, including mCRPC, but it has low and restricted expression in normal tissues (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). This differential in expression provides a mechanism by which targeted therapeutic radiation can be delivered to cancer cells via PSMA while minimizing radiation-related side effects. PSMA-targeted RLT utilizes a radiolabeled small-molecule ligand that targets and binds with high affinity to PSMA, resulting in internalization and retention within the targeted PC cell (Ghosh and Heston 2004, Benešová et al 2015), to treat PSMA-positive mCRPC.

^{177}Lu-PSMA-617 has been used experimentally in the clinic since 2013 for the treatment of patients with mCRPC (Ahmadzadehfar et al 2015). As a result, published data on efficacy (and safety) of ^{177}Lu-PSMA-617 in patients with mCRPC is available from many centers. Moreover, PSMA ligand can be also radiolabeled with gallium-68 (^{68}Ga) and used to identify PSMA expression and determine the local extent of disease by PET imaging. Therefore, ^{68}Ga-PSMA-11 PET/CT imaging is used as a component of eligibility criteria.

While the efficacy results from the retrospective studies are encouraging, the data from the prospective studies are important as these studies involved well-defined inclusion/exclusion criteria, careful patient selection via ^{68}Ga-PSMA-11 and FDG PET/CT imaging, and prespecified data collection and analysis (Emmett et al 2019, Violet et al 2020, Hofman et al 2021).

2.2. About the product

PSMA-617, the non-radioactive precursor molecule, consists of the PSMA-binding ligand glutamate-urea-lysine, a DOTA-chelator, and a linker connecting these 2 entities. This is then complexed with the lutetium radionuclide, and the radioactive nature of lutetium-177 is responsible for the therapeutic activity of ^{177}Lu-PSMA-617.

The mechanism of action of ^{177}Lu-PSMA-617 is to deliver therapeutic radiation to prostate cancer cells via its binding to PSMA.

By design, ^{177}Lu-PSMA-617 exhibits high PSMA binding affinity and internalization, prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015) that was further supported by published dosimetry studies (Delker et al 2016, Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017, Yadav et al 2017).

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

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

The relevant pharmacotherapeutic group is "Other therapeutic radiopharmaceuticals" (ATC code: V10XX05).

The initially applied indication for lutetium (^{177}Lu) vipivotide tetraxetan was for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

The finally agreed indication is Pluvicto in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition 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.

The recommended treatment regimen of Pluvicto is 7 400 MBq intravenously every 6 weeks (±1 week) for up to a total of 6 doses, unless there is disease progression or unacceptable toxicity.

Pluvicto should be administered only by persons authorised to handle radiopharmaceuticals in designated clinical settings (see section SmPC 6.6) and after evaluation of the patient by a qualified physician.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that approved treatments exist for (at least) part of the target population and that other comparable ^{177}Lu-PSMA products are available in clinical practice in the EU.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection/infusion. One mL of solution contains 1 000 MBq of lutetium (^{177}Lu) vipivotide tetraxetan at the date and time of calibration as active substance.

The total amount of radioactivity per single-dose vial is 7 400 MBq ± 10% at the date and time of administration. Given the fixed volumetric activity of 1 000 MBq/mL at the date and time of calibration, the volume of the solution in the vial can range from 7.5 mL to 12.5 mL in order to provide the required amount of radioactivity at the date and time of administration.

Other ingredients are: acetic acid, sodium acetate, gentisic acid, sodium ascorbate, pentetic acid (DTPA), and water for injections.

The product is available in clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal.

2.4.2. Active Substance

General information

The manufacture of the active substance Lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617) involves a radionuclide precursor (Lutetium (^{177}Lu) chloride) and a cold chemical precursor (vipivotide tetraxetan, or PSMA-617).

During evaluation, it was considered that the provided description of the manufacturing of the radionuclide precursor Lutetium-177 chloride for radiolabelling in part S.2.3 provides only an abstract of its manufacturing process. As result of the key role of the radionuclide precursor Lutetium-177 its manufacturing process should be detailed documented, according to the guideline on radiopharmaceuticals, it was requested to provide this information as a separate complete modules 3.2.S or alternatively, in an ASMF as Major Objection (MO). The applicant informed that the precursor Lutetium-177 used in this marketing authorisation application is the same that for the marketing authorisations for Lumark and EndolucinBeta (both authorised centrally) except in view to the radioactive concentration. Considering that the radionuclide precursor [^{177}Lu]Lutetium chloride used is manufactured from the same starting material sources and the same manufacturing lines / procedures under the same standards inclusive GMP and specifications where the authorised products Lumark and EndolucinBeta are manufactured, except in view to the radioactive concentration and absolute radioactive amount the quality of the radionuclide precursor [^{177}Lu]Lutetium chloride is sufficiently assured and no need to provide more information is considered necessary.

In line with the Guideline on Radiopharmaceuticals a separate module 3.2.S is presented for the cold radioactive chemical precursor vipivotide tetraxetan.

Lutetium (^{177}Lu) vipivotide tetraxetan

The chemical name of Lutetium (^{177}Lu) vipivotide tetraxetan is 2-[4-[2-[[4-[[(2S)-1-[[(5S)-5-carboxy-5-[[(1S)-1,3-dicarboxypropyl]carbamoylamino]pentyl]amino]-3-naphthalen-2-yl-1-oxopropan-2-yl]carbamoyl]cyclohexyl]methylamino]-2-oxoethyl]-4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetate; lutetium-177(3+) corresponding to the molecular formula

$C_{49}H_{68}{}^{177}LuN_9O_{16}$. It is also referred to in the dossier as ^{177}Lu-PSMA-617. It has a relative molecular mass of 1216.06 g/mol and the following structure:

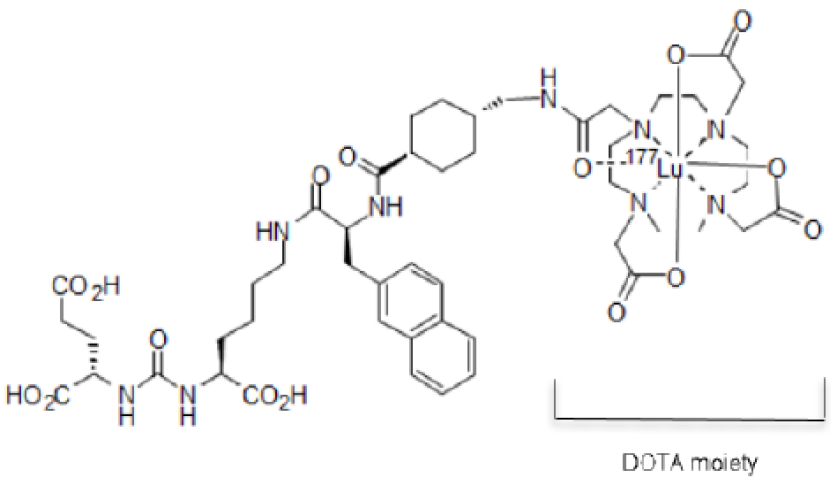


Figure 1: Lutetium (^{177}Lu) vipivotide tetraxetan structure

The chemical structure of Lutetium (^{177}Lu) vipivotide tetraxetan was elucidated by using suitable tests.

The active substance is a clear, colorless to slightly yellow solution. The solubility is not available as the Lutetium (^{177}Lu) vipivotide tetraxetan is not isolated in the manufacturing process.

Lutetium (^{177}Lu) vipivotide tetraxetan exhibits stereoisomerism

Polymorphism has not been observed.

The maximum beta energy for the decay of ^{177}Lu to ^{177}Hf is 497 keV. The average beta energy is approximately 130 keV. Lutetium-177 emits several gamma rays useful for imaging. The significant energies and abundance of these gamma rays are 112.9 keV (6.2 %) and 208.4 keV (10.4 %).

Manufacture, characterisation and process controls

Lutetium (^{177}Lu) vipivotide tetraxetan is manufactured by one manufacturer

The radioactive active substance Lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617) is produced as an aqueous concentrated solution (mother solution) manufactured by radiolabeling of chemical precursor vipivotide tetraxetan (PSMA-617) with the radioactive starting material Lu-177 chloride. It has been used as a starting materials with well defined specifications. The synthesis of ^{177}Lu-PSMA-617 is performed in the self-contained closed-system synthesis module which is automated and remotely controlled by GMP compliant software and automated monitoring and recording of the process parameters. The synthesis of ^{177}Lu-PSMA-617 and its formulation into ^{177}Lu-PSMA-617 solution for injection/infusion finished product is part of an automated continuous process which does not allow for isolation and testing of the active substance due to its radioactive decay.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process, which does not allow for isolation and testing of the pure active

substance. Therefore all information related to impurities has been consolidated in finished product section.

At the end of synthesis, the active substance is collected in a 30 mL sterile recovery vial in the dispensing cell Grade A. The container closure system consists of a sterile 30 mL Type I glass vial compliant with Ph. Eur. 3.2.1. This vial is the same vial as the primary packaging of the drug product

Specification

The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process, which does not allow for isolation and testing of the pure active substance. Specifications are therefore available for the finished product only.

Stability

The synthesis of the active substance and its formulation into the finished product are part of an automated continuous process, which does not allow for isolation and testing of the pure drug substance. Stability information is therefore provided for the finished product only.

Cold chemical precursor: vipivotide* tetraxetan *(PSMA-617).

The chemical name of the cold chemical precursors vipivotide tetraxetan is (3S,10S,14S)-3-[(Naphthalen-2-yl)methyl]-1,4,12-trioxo-1-[(1r,4S)-4-({2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]acetamido}methyl)cyclohexyl]-

2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid corresponding to the molecular formula $C_{49}H_{71}N_9O_{16}$. It has a relative molecular mass of 1042.14 and the following structure:

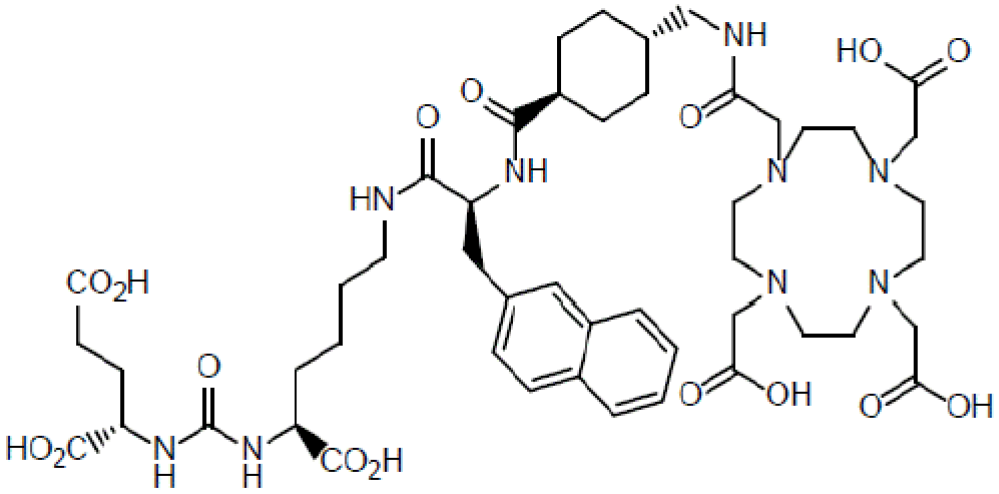


Figure 2: Cold chemical precursors vipivotide tetraxetan (PSMA-617) structure

The chemical structure was elucidated by a combination of MS, IR, ^{1}H-NMR, and ^{13}C-NMR.

The cold chemical precursor is a non-hygroscopic white to off-white solid, slightly soluble (in water.

Vipivotide textran exhibits stereoisomerism due to the presence of 3 chiral centres.

Polymorphism has not been observed for the active substance.

Manufacture, characterisation and process controls

The cold precursor is manufactured by one manufacturing site.

Vipivotide textran (PSMA-617) is synthesized in 6 main steps using commercially available well defined starting materials with acceptable specifications. The synthesis consists in the synthesis of the intermediates , preparation of bulk vipivotide tetraxetan by purificationand lyophilization, and finally preparation of vipivotide tetraxetan lyophilisate in vial-by-vial fill and lyophilization.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the chemical precursor and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The chemical precursor is packaged in polypropylene copolymer bottles with a polypropylene closure. which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The cold chemical precursor specifications include tests for appearance (visual), identity (ESI-MS, IR), assay (HPLC), impurities (HPLC), enantiomeric purity (GC-MS), residual solvents (GC), elemental impurities (ICP-MS), and water content (GC)- The Aliquot in vial specifications includes in addition the Net peptide (HPLC) and microbiology.

The reporting threshold and limits for individual and total impurities in vipivotide tetraxetan are as presented in the European Pharmacopoeia General Monograph 2902, Chemical Precursors for Radiopharmaceutical Preparations.

Ssolvents used in the later steps of the process are tested to assess the levels as part of the bulk specifications

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data 9 commercial and pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 and 6 commercial scale batches in bulk and aliquot in vials respectively of vipivotide tetraxetan from the proposed manufacturer stored in the intended commercial package for up to 36 months data for the bulk, long-term storage condition of -20°C.For the vials, 36 months data are available at intermediate storage conditions of 5°C. In addition, stability studies have been performed at accelerated conditions (40°C / 75 % RH and 50 °C/75 % RH) over 14 days.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

The stability data demonstrate no evidence of any significant physical or chemical changes at the long-term storage condition of -20°C. Based on the long-term stability data, the storage temperature for both bulk and aliquot in vials is proposed as -20°C with a re-evaluation date of 36 months.

36 months stability data from six validation batches of the aliquot in vials at the intermediate (5°C) storage condition are further provided. The intermediate stability data demonstrate no evidence of any significant physical or chemical changes when stored at 5°C. The intermediate stability data establishes that the aliquot in vials when stored refrigerated (5°C) can be held for 36 months prior to radiolabelling.

Fourteen days stability data, Aliquot in vials at accelerated (40°C/75 % RH and 50°C/75 % RH) storage conditions are provided. Based on this stability data, vipivotide tetraxetan that is held for a short period of time at elevated temperatures during shipping or radiolabelling remains within the appropriate quality attributes as described in for up to 14 days at 40°C ± 2°C and up to 3 days at 50°C ± 2°C.

Forced degradation studies in one batch were conducted under stress conditions to evaluate the possible degradants of vipivotide tetraxetan generated. Degradation products increased under accelerated conditions but remained within the specification.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months The reported stability studies support a 36-month re-test period when stored at -20°C in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as clear, colourless to slightly yellow solution.

The finished product was developed as a ready to use radiopharmaceutical solution for injection/infusion containing the active substance with a volumetric activity of 1000 MBq/mL at reference date and time (calibration time (tc)). .

The compatibility of the active substance with the excipients has been demonstrated throughout the batch analyses and the stability studies performed on the finished product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except acetic acid, sodium acetate and gentisic acid which comply with In house specifications. Pentetic acid is compliant with USP/NF. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC .

The overall manufacturing process developed involves an automated continuous process, where the synthesis of the active substance is also part of the finished product manufacturing process and follows conventional drug compounding and aseptic filling methods commonly used in the pharmaceutical industry. During the manufacturing process development of the finished product, critical process parameters were identified, evaluated and optimized. These efforts aimed at achieving a stable finished product with a suitable method of sterilization while maintaining the integrity of the finished product.

The finished product is a ready to use radiopharmaceutical product provided in a single dose vial for slow intravenous administration.The primary packaging is clear, colourless type I glass vial, closed with a bromobutyl rubber stopper and aluminium seal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The active substance is manufactured by one manufacturing site.

The finished product manufacturing process consists of 8 main steps: preparation of the dispensing cell and dilution solution, measurement of volumetric activity and transfer, formulation of the bulk solution, homogenization of the bulk solution, final sterilizing filtration and dispensing of the finished product, measurement of weight and radioactivity of the finished product vial, andloading into shielded secondary container. The process is considered to be a non-standard manufacturing process.

The manufacturing process of the finished product has been validated using six full-scale production batches which have been processed in the same manufacturing facilities using the same process and the same type of equipment as for the batches intended for commercial supply.

All six batches fully met the quality control specifications. The in-process data and the results from additional testing demonstrated that the manufacturing process is robust and consistently yields a product capable of meeting the pre-defined quality characteristics. The in-process controls are adequate for this type of manufacturing process.

Validation studies have been performed to demonstrate the suitability of manufacturing conditions in order to guarantee consistent and reproducible quality of the finished product at the manufacturing site.

Product specification

The finished product release and stability testing specifications include appropriate tests for this kind of dosage form: appearance (visual), pH, (Ph. Eur.), assay (UV, RP-UV-HPLC), chemical purity (peptide purity) (RP-UV-HPLC), radiochemical purity (RP-γ β-HPLC, ITLC, Gamma spectrometry), identification (RP-γ β-HPLC), specific activity (HPLC), volumetric activity (dose calibration/balance), filter integrity (Ph. Eur.), radionuclide identity half time determination (dose calibration), bacterial endotoxins (Ph. Eur.), and sterility (Ph. Eur.)

The total amount of radiochemical impurities is limited to ≤ 5 % at the end of shelf-life which is in conformity with the guideline on radiopharmaceuticals. No impurities generated during the manufacturing process of the active substance and the finished product have been observed above the specification limit, in any of the batches addressed.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP/OES method was provided, demonstrating that each relevant elemental impurity was not detected above the limit of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 6 commercial scale batches of finished product stored for up to 5 days under long term conditions (5 ± 3°C, 25 ± 2°C), intermediate conditions (30 ± 2°C) and accelerated conditions (40 ± 2°C)) according to the ICH guidelines were provided. The batches of the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested per the stability indicating specifications: the parameters tested and analytical methods used were stability indicating.
The finished product did not show any significant changes whilst stored during 5 days at 5 ± 3°C, 25 ± 2°C, 30 ± 2°C, 40 ± 2°C Under these conditions, all the physical-chemical and microbiological results comply with the specifications until the end of the shelf-life.

Gentisic acid and sodium ascorbate are known to be photosensitive substances. However, photostability testing was not performed as the finished product is intended to be stored in its secondary packaging (made of lead pot) until end of shelf-life including the administration timeframe due to radiation-safety purposes. Based on this assessment the photostability risk degradation is considered negligible and photostability has not been further investigated nor included in the stability protocol. This was considered satisfactory.

Based on available stability data, the proposed shelf-life of 120 hours (5 days) from the date and time of calibration and store in the original package in order to protect from ionising radiation (lead shielding) as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

One MO has been raised to provide information of the manufacturing process of the radionuclide precursor Lutetium-177 as a separate complete module 3.2.S or alternatively, in an ASMF. The applicant informed that Lutetium-177 used in this application is the same that for the marketing authorizations for Lumark and EndolucinBeta (both authorized centrally). Considering that the quality of the precursor is sufficiently assured, no need to provide more information was considered necessary.

Overall, during the procedure, the information of the dossier has been updated and improved as requested.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The proposed indication is the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy. ^{177}Lu vipivotide tetraxetan, also referred to as [^{177}Lu]Lu-PSMA-617 or ^{177}Lu-PSMA-617, is PSMA-targeted radioligand therapy developed to treat mCRPC.

PSMA is a type II transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II, and has been confirmed as a biological target for therapy in prostate cancer. PSMA is highly expressed in nearly all prostate cancers, but has restricted and several hundred-fold lower expression in some normal tissues such as the duodenal mucosa, renal proximal tubules, and salivary glands. Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, androgen-independent prostate cancer. The differential expression of PSMA from tumour to non-tumour tissue supports targeted strategies involving radiotherapeutic intervention.

The non-clinical program has been designed according to ICH (International Council for Harmonisation) S9 guideline on non-clinical evaluation for anticancer pharmaceuticals and CHMP Guideline on the nonclinical requirements for radiopharmaceuticals (EMA/CHMP/SWP/686140/2018).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

PSMA is expressed in nearly all prostate cancers, and its overexpression correlates with a metastatic and hormone-refractory condition. ^{177}Lu-PSMA-617 is a PSMA-targeted radioligand therapy developed for mCRPC treatment. The PSMA-617 molecule consists of three components: the PSMA-targeting pharmacophore glutamate-urea-lysine, the metal chelator DOTA, and a linker connecting these two moieties. Lu-177 is the radionuclide incorporated into the DOTA chelator of PSMA-617, and its radioactivity is responsible for the therapeutic activity of ^{177}Lu-PSMA-617. The mechanism of action of ^{177}Lu-PSMA-617 is thus to deliver therapeutic radiation to cancer cells via its binding to PSMA.

The binding affinity of PSMA-617 and the non-radioactive ^{nat}Lu-labelled PSMA-617 in LNCaP (Lymph node carcinoma of the prostate) cells was in nanomolar range (Ki = 2.34±2.94 nM for unlabelled PSMA-617, and Ki = 6.91±1.32 nM for the lutetium complex). The in vitro uptake of ^{177}Lu-PSMA-617 into PSMA-positive PC-3 PIP tumour cells was approximately 55–70%, and the internalised fraction was about 10 to 15% of total added radioactivity. In contrast, the uptake in PSMA-negative PC-3 flu

tumour cells did not exceed 0.5%. PSMA-dependent uptake of ^{177}Lu-PSMA-617 was confirmed in vivo in mice bearing both PSMA-positive PC-3 PIP and -negative PC-3 flu prostate cancer xenografts. Initial high uptake in kidneys was quickly cleared. PSMA-specific uptake was further demonstrated in LNCaP tumour xenografts in mice as ^{177}Lu-PSMA-617 uptake in these PSMA-positive tumours could be blocked by the selective PSMA inhibitor 2-(phosphonomethyl)pentanedioic acid.

The Lu-177-induced cancer cell death is the result of both direct effects of radiation on cellular DNA, as well as indirect DNA-damaging effects from reactive species formed from upon irradiation. The physical half-life of Lu-177 is 6.647 days combined with the intratumoural retention of ^{177}Lu-PSMA-617 allows for the continued irradiation of the lesions. A maximal radiation penetration of less than 2 mm into tissues ensures a reduced exposure to neighbouring normal cells. ^{177}Lu-PSMA-617 exhibited in vitro cytotoxicity in PSMA-positive PC-3 PIP cells but not in PSMA-negative PC-3 flu cells. In vivo, C57BL/6 immunocompetent mice bearing tumour xenografts created from murine prostate cancer cell lines that have been transfected to express human PSMA (RM1-hPSMA) exhibited a specific activity-dependent increase in tumour uptake after treatment with ^{177}Lu-PSMA-617 at different formulations for high, intermediate or low specific activity (corresponding to low, intermediate and high amount of mass having the same level of total radioactivity). This improved biodistribution resulted in improved anti-tumour activity demonstrated as a decrease in tumour volume and an increase in overall survival. Higher specific activity treatments caused more DNA double-strand breaks. When radioactivity levels were varied in high specific activity formulation, ^{177}Lu-PSMA-617 treatment led to dose-dependent therapeutic activity in the RM1-PGLS mouse model of prostate cancer.

2.5.2.2. Secondary pharmacodynamic studies

At the concentration of 10 µM, ^{175}Lu-PSMA-617 was found not to interact with a panel of 87 potential different targets (receptors, ion channels, enzymes and transporters). This concentration is approximately 132-fold higher than the theoretical clinical Cmax of the total PSMA-617 in patients (around 76 nM) following an administration of ^{177}Lu-PSMA-617. ^{175}Lu-PSMA-617 (cold-labelled) and PSMA-617 (unlabelled) exhibited no cytotoxic effect on PSMA-positive or PSMA-negative human cancer cell lines at the concentrations up to 10 µM suggesting that cytotoxicity of ^{177}Lu-PSMA-617 (as described in section 2.5.2.1 Primary pharmacodynamic studies) is dependent on the presence of the radioactive Lu-177.

2.5.2.3. Safety pharmacology programme

A ^{175}Lu-PSMA-617/PSMA-617 solution (1:1) at the concentrations of 1, 10 and 100 µM (total PSMA-617 content) inhibited hERG tail current by 8±4%, 8±0%, and 13±2%, respectively. The control analytical measurements revealed the PSMA-617 concentration to be out of range. Thus, the cells were underexposed to PSMA-617 between 68.64% and 88.03% of the nominal concentrations (i.e. 0.34 µM and 44 µM). Nevertheless, given the theoretical clinical Cmax of ca. 76 nM the highest concentration used in this assay was ca. 580-fold higher than the theoretical clinical Cmax, and no clinically relevant hERG inhibition is expected

In vivo GLP safety pharmacology studies were performed in rats and minipigs. Rovenska et al 2008 showed that PSMA is expressed in rats, minipigs and humans, is highly conserved and has similar enzymatic activity across the species. Therefore, rats and minipigs are considered pharmacologically relevant species. A ^{175}Lu-PSMA-617 solution (containing the non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617) had no effect on general behaviour parameters (Irwin test) in male Sprague-Dawley rats after single intravenous administration at doses up to 1.8 mg/kg. An intravenous ^{175}Lu-PSMA-617 solution did not influence respiratory function of the conscious male Sprague-Dawley rats up

to 1.8 mg/kg. No effects of this test item on cardiovascular system were observed in conscious telemetered minipigs up to 1.0 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted as lutetium vipivotide tetraxetan is targeted to PSMA, which is specifically expressed in prostate cancer.

2.5.3. Pharmacokinetics

Tissue biodistribution studies were conducted with ^{177}Lu-PSMA-617 in a mouse tumour model and in healthy rats. In these studies, the test article was a ^{177}Lu-PSMA-617 formulation resembling the one used in humans. This test formulation contains both ^{177}Lu-PSMA-617 as well as unlabelled PSMA-617, as not all PSMA-617 molecules are radiolabelled with Lu-177 following the chelation procedure. In vitro studies were performed to characterise plasma protein binding, blood-to-plasma distribution, and metabolic stability of non-radioactive ^{175}Lu-PSMA-617 and the unlabelled PSMA-617 precursor (as a surrogate for ^{177}Lu-PSMA-617 formulation) in the animal toxicity species (rat and minipig) and in human.

2.5.3.1. Methods of analysis

The analytical methods for quantification of ^{175}Lu-PSMA-617 and PSMA-617 in vehicle by LC-UV, in Tyrode's solution by HPLC-UV and in rat and minipig plasma by LC-MS/MS were developed and in general successfully validated under GLP conditions as most of the acceptance criteria for validation were met. For the methods to determine ^{175}Lu-PSMA-617 and PSMA-617 in vehicle and Tyrode's solution, linearity was shown in a narrower concentration range than the quantification range of the method. However, the samples were diluted to fall within the range of the calibration curve. During development of the bioanalytical method in rat plasma, a carryover effect was observed in roughly a quarter of the validation samples. Therefore, preventive measures have been applied during bioanalytical measurements in toxicokinetic studies, i.e. blank samples were inserted after samples likely to have high concentrations. This is acceptable. Upon development of the bioanalytical method for PSMA-617 in minipig plasma, a matrix effect was observed at the QCH level and a possible impact of this effect cannot be ruled out completely.

2.5.3.2. Absorption

Classical pharmacokinetics describing compound plasma levels was investigated within toxicokinetic studies in rats and minipigs using non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617 and is described in detail in Toxicology section.

2.5.3.3. Distribution

The in vitro plasma protein binding of non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617 to human, rat and minipig plasma was found to be moderate for both compounds, with the highest values observed in human. In the case of ^{175}Lu-PSMA-617, the protein binding varied between 62 and 70% in human, between 52 and 60% in rat, and 57 and 63% in minipig plasma. For PSMA-617, it was 58–70% in human, 47–59% in rat, and 54– 58% in minipig plasma.

^{175}Lu-PSMA-617 and unlabelled PSMA-617 both did not preferentially distribute into erythrocytes as the mean blood-to-plasma ratios were below 1 (^{175}Lu-PSMA-617: 0.34 for mouse, 0.45 for rat, 0.43 for

dog, 0.55 for minipig, and 0.49 for human; PSMA-617: 0.40 for mouse, 0.35 for rat, 0.96 for dog, 0.42 for minipig, and 0.28 for human).

In vivo, ^{177}Lu-PSMA-617 quickly accumulated in PSMA-positive PC-3 PIP tumour xenografts of female athymic nude Balb/c mice up to a maximum of 56.0±8.0% injected activity /g after 4 h post-injection. On the contrary, in PSMA-negative PC-3 flu tumours of the same animals the accumulated radioactivity was clearly below the blood level, indicating PSMA-specific accumulation of the radioligand. The initial uptake of in the kidneys was cleared quickly, resulting in renal retention of ca. 3% injected activity /g after 6 h post-injection.

In normal male Wistar rats, the radioligand was rapidly cleared from blood with distribution at the initial time point in liver, intestine, kidneys, muscle and skeleton. Despite initial accumulation of radioactivity in blood and muscle, it was completely cleared at 24 h post-injection. Retention of residual radioactivity was observed in the intestine, liver, kidneys and skeleton at 24 h. However, uptake in these organs, except skeleton, gradually decreased over time. In contrast, the amount of radioactivity in the skeleton remained constant up to 7 days post-administration. As no uptake and no retention of radioactivity was observed in normal bone in patients, the observation of persistent accumulation and retention of ^{177}Lu-PSMA-617 in the skeleton of rats is considered not to be clinically relevant.

The effect of injected peptide amounts on the biodistribution of ^{177}Lu-PSMA-617 was studied in healthy male Sprague-Dawley rats after single intravenous bolus tail vein injection. Three different peptide doses (unlabelled PSMA-617) were evaluated (0.21, 2.1 and 21 µg) resulting in peptide amounts of 1.1±0.1, 9.8±0.9, 109.3±13.7 µg/kg rat body weight, which corresponds to a human dose of 74±7, 683±60, 7654±961 µg/70 kg body weight, respectively. No differences in the blood clearance of ^{177}Lu-PSMA-617 were observed, it was comparable with half-lives of 0.49 hours, 0.49 hours, and 0.5 hours for the different peptide amounts (0.21, 2.1 and 21 µg), respectively. The distribution of ^{177}Lu-PSMA-617 was unspecific for all doses, with the exception of the kidneys. There was no uptake in the brain. ^{177}Lu-PSMA-617 exhibited high initial accumulation in the kidneys; however, the radioactivity was rapidly eliminated. The kidney uptake was decreased with increasing peptide amount (1.1 µg/kg body weight – 36.6±12.9%, 9.8 µg/kg body weight – 6.2±0.5%, 109.3 µg/kg body weight – 1.8±0.1% injected dose, respectively).

2.5.3.4. Metabolism

Non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617 were found to be metabolically stable in human, rat and minipig plasma (for 2 h) and in liver and kidney S9 fractions (for 60 min.) of the same species at 37 °C. Lauric acid chosen by the Applicant as a positive control in metabolic assays in kidney S9 fractions shows the highest turnover (lauric acid hydroxylation) compared to other substrates such as NADPH cytochrome c reductase or glucuronidation of 4-methylumbelliferone. Compound loss measured in the positive controls in study 0591 were within or above the rate specified in the product specification.

2.5.3.5. Excretion

In healthy male Sprague-Dawley rats, ^{177}Lu-PSMA-617 specifically accumulated only in the kidneys but was not retained there as the radioactivity was rapidly eliminated. After 24 h, only 0.4% injected dose was found in the kidneys, and more than 97% injected dose was present in the urine. Similar findings were obtained in male Wistar rats, which excreted >80% of the injected ^{177}Lu-PSMA-617 radioactivity within 3 hours via renal route.

2.5.3.6. Pharmacokinetic drug interactions

In vitro studies of the potential of the ^{175}Lu-PSMA-617 test solution (a mixture of ^{175}Lu-labeled PSMA-617 and unlabelled PSMA-617) to inhibit cytochrome P450 enzymes in human liver microsomes revealed that the test item is not a reversible or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4, as the IC_{50} values could not be determined.

The EC_{50} values for induction of CYP1A2, 2B6 and 3A4 metabolic activity by the ^{175}Lu-PSMA-617 test solution as specified above were determined as of 16.6, 50.7 and 1.57 μg/mL, respectively. This corresponds to 15.9, 48.6 and 1.5 μM PSMA-617, which exceeds the theoretical clinical C_{max} of ca. 76 nM more than 19-fold. Therefore, no clinical relevance is expected.

The induction potential was evaluated on activity level, and not primarily on mRNA level as suggested by the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

In vitro drug interaction studies with transporters showed that ^{175}Lu-PSMA-617 solution is not an inhibitor of P-gp, BCRP, BSEP, MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3. ^{175}Lu-PSMA-617 solution was found to be not a substrate of P-gp, BCRP, MATE1, MATE2-K, OCT2, OAT1, and OAT3.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Toxicology of a non-radioactive mixture of ^{175}Lu-PSMA-617 and unlabelled PSMA-617 (1:1) was assessed in extended single dose toxicity studies in rats and minipigs.

At single iv doses up to 4.0 mg/kg in the rat and 1.8 mg/kg in the minipig, no mortality and no major adverse effects were observed. In the rat, only minor changes with respect to haematological and biochemical aspects occurred. Only one female animal of the high dose group revealed macroscopic and microscopic changes of the right kidney (single, pale area with unilateral M-nephroblastoma). This might be an incidental or spontaneous effect but in view of the fact that the kidneys are a primary site of PSMA uptake and that ^{177}Lu-PSMA-617 is rapidly excreted through the kidneys, it cannot be excluded that nephrotoxicity might be a serious adverse event after repeated treatment in the clinical setting. The NOAEL was considered to be 4.0 mg in the rat study, which represents a safety margin of 150 based on body surface area scaling relative to the maximum potential human dose of 275 µg.

In the minipig, no treatment related changes were noted with the exception of adverse effects at the injection site: minimal or mild acute inflammation associated with vascular and perivascular necrosis was seen in animals treated at all doses. The NOAEL was set 1.8 mg/kg, which corresponds to an approximately 400-fold safety margin, based on body surface area scaling relative to the maximum potential human dose of 275 µg.

However, in the in vitro pharmacology study Cmax was calculated after a bolus injection of 200 µg and not 275 µg.

The estimated exposure multiples of the single-dose toxicity studies (150 and 400 in rats and minipigs, respectively) were based on the potential maximum human dose of 275 µg whereas the maximum theoretical concentration value (Cmax) in the in vitro secondary pharmacology study (Study 100053460-4) was calculated after a bolus injection of 200 µg. The 275 µg mass dose provides the most conservative estimate and provides a safety margin of 132-fold. Due to the discrepancy between the two studies, this value was recalculated using the 200 mg mass dose leading to a 94-fold margin instead of the initial calculated 132-fold margin. This new value provides a sufficient margin.

2.5.4.2. Repeat dose toxicity

In the 4-week repeat-dose toxicity study in Sprague-Dawley rats, unlabelled PSMA-617 was administered once a week via the intravenous route for up to 23 days (total of 4 administrations). The doses were 0, 0.04, 0.16 and 0.40 mg/kg. There was no mortality associated with PSMA-617. A slight increase in the relative weight for testis and kidney at the highest dose tested was recorded as well as a minimal decrease of monocytes and creatinine. Microscopic changes such as inflammation in the kidney or lymphocytic infiltration in the epididymides were recorded but were of low incidence. The NOAEL was set 0.4 mg/kg, which represents a safety margin of 15 based on body surface area scaling relative to the maximum potential human dose of 275 µg. The results underline the assumption that PSMA-617 is well tolerated. No TK data were collected and no recovery period was included in the study.

2.5.4.3. Genotoxicity

Unlabelled PSMA-617 was negative for genotoxicity in a bacterial mutagenicity assay. However, given that the human drug product is radiolabelled, genotoxicity is expected.

2.5.4.4. Carcinogenicity

Carcinogenicity studies have not been conducted with ^{177}Lu-PSMA-617, the unlabelled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617 as they are not required according to the relevant guidelines.

2.5.4.5. Reproductive and developmental toxicity

Studies on reproductive and developmental toxicity have not been performed with ^{177}Lu-PSMA-617, the unlabelled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617 and are not required for an anticancer radioactive agent due to the radioactive nature of ^{177}Lu and thus its DNA reactivity, which would likely result in toxic reproductive and developmental effects. This is in accordance with the ICH S9 guidance, CHMP draft guidance (EMA/CHMP/SWP/686140/2018) and Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations Guidance for Industry, Center for Drug Evaluation and Research (CDER) August 2019. In addition, since men are the intended patient population, the complete program of reproductive toxicity studies is per se not required.

Considering the maximum radiation absorbed dose to the testes of 6.22 Gy ^{177}Lu-PSMA-617 has the potential to cause infertility in male patients.

2.5.4.6. Toxicokinetic data

2.5.4.7. Local Tolerance

No dedicated local tolerance studies were performed. The local tolerance after iv administration is considered adequately assessed in the performed iv single and repeat-dose toxicology studies.

2.5.5. Ecotoxicity/environmental risk assessment

Assuming one treatment per year, resulting in maximal 6 applications, the PECsurfacewater can be calculated to 0.000023 µg/L. Consequently, a Phase II assessment is not necessary.

Table 1: Summary of main study results

Substance (INN/Invented Name): Lutetium (^{177}Lu) vipivotide tetraxetan			
CAS-number (if available): 1703749-62-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	literature	<4.5	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (treatment regime)	0.000023	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)	radioactive		(Y)

2.5.6. Discussion on non-clinical aspects

Pharmacology

PSMA overexpression is specifically localised in prostate cancers and correlates with a metastatic and hormone-refractory disease. Lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617) is a PSMA-targeted radioligand therapy developed for treatment of metastatic castration-resistant prostate cancer. The mechanism of action of ^{177}Lu-PSMA-617 is to deliver therapeutic radiation from Lu-177 selectively to cancer cells via the high affinity binding to PSMA. ^{177}Lu-PSMA-617 was demonstrated to specifically accumulate in PSMA-positive prostate cancer cells in vitro and in PSMA-positive tumours in vivo. Initially high uptake in kidneys was quickly cleared. The compound exhibited in vitro cytotoxicity only in PSMA-positive cancer cells. Mice bearing tumour xenografts created from murine prostate cancer cell lines that have been transfected to express human PSMA (RM1-hPSMA) showed a specific activity-dependent increase in tumour uptake after treatment with ^{177}Lu-PSMA-617, which resulted in a decrease in tumour volume and an increase in overall survival. Furthermore, the compound demonstrated a dose-dependent therapeutic activity in the RM1-PGLS mouse model of prostate cancer. ^{175}Lu-PSMA-617 had no off-target activity further confirming its high selectivity for PSMA. ^{175}Lu-PSMA-617 (cold-labelled) and PSMA-617 (unlabelled) were both not cytotoxic in PSMA-positive or PSMA-negative human cancer cell lines suggesting radioactivity-dependent cytotoxicity of ^{177}Lu-PSMA-617. A ^{175}Lu-PSMA-617/PSMA-617 solution (1:1) did not inhibit hERG tail current in vitro and had no effects on central nervous, cardiovascular and respiratory systems in rats and minipigs that are considered pharmacologically relevant models.

Pharmacokinetics

The analytical methods for quantification of ^{175}Lu-PSMA-617 and PSMA-617 in vehicle by LC-UV, in Tyrode's solution by HPLC-UV and in rat and minipig plasma by LC-MS/MS were developed and in general successfully validated under GLP conditions. For the methods to determine ^{175}Lu-PSMA-617 and PSMA-617 in vehicle and Tyrode's solution, linearity was shown in a narrower concentration range than the quantification range of the method. However, samples were diluted to fall into the range of the calibration curve. Upon development of the bioanalytical method for PSMA-617 in minipig plasma, a matrix effect was observed at the QCH level and a possible impact of the matrix effect cannot be ruled out completely. However, as matrix effects are more likely at lower analyte concentrations, the Applicant presumed that the occurrence of the matrix effect at QCH for PSMA-617 may be due to an error in the preparation of Matrix Factor samples. The matrix effect was not observed for [^{175}Lu]Lu-PSMA-617. Nevertheless, the PK parameters were comparable between [^{175}Lu]Lu-PSMA-617 and PSMA-617. Thus, it was concluded that the relevance for the conclusions of the TK study is negligible.

The in vitro plasma protein binding of non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617 to human, rat and minipig plasma was moderate. Both compounds did not preferentially distribute into

erythrocytes as the mean blood-to-plasma ratios were below 1. In vivo, ^{177}Lu-PSMA-617 quickly accumulated in PSMA-positive PC-3 PIP tumour xenografts of mice but not in concomitantly present PSMA-negative PC-3 flu tumours. The initial uptake in the kidneys was cleared quickly. In healthy rats, the radioligand was rapidly cleared from blood and distributed to liver, intestine, kidneys, muscle and skeleton. However, uptake in these organs, except skeleton, gradually decreased over time. The amount of radioactivity in the skeleton remained constant up to 7 days post-administration. As no uptake and no retention of radioactivity was observed in normal bone in patients, the observation of persistent accumulation and retention of ^{177}Lu-PSMA-617 in the skeleton of rats is not clinically relevant. Animal distribution studies clearly pointed out at primarily renal excretion of the drug.

Non-radioactive ^{175}Lu-PSMA-617 and unlabelled PSMA-617 were found to be metabolically stable in human, rat and minipig plasma and in liver and kidney S9 fractions of the same species. Lauric acid chosen by the Applicant as a positive control in metabolic assays in kidney S9 fractions shows the highest turnover (lauric acid hydroxylation) compared to other substrates such as NADPH cytochrome c reductase or glucuronidation of 4-methylumbelliferone. Compound loss measured in the positive controls in study 0591 were within or above the rate specified in the product specification. Therefore, the choice of the positive control is considered justified.

The Applicant could not explain the observed loss of PSMA-617. However, no depletion of the cold [^{175}Lu]Lu-PSMA-617 was noted. It is agreed that [^{175}Lu]Lu-PSMA-617 is a more suitable surrogate of [^{177}Lu]Lu-PSMA-617. Moreover, in humans [^{177}Lu]Lu-PSMA-617 turned out to be metabolically stable both in systemic circulation and the kidneys.

A ^{175}Lu-PSMA-617 test solution (a mixture of ^{175}Lu-labeled PSMA-617 and unlabelled PSMA-617) is not a reversible or time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. It did not induce CYP1A2, 2B6 and 3A4 metabolic activity to a clinically relevant extent.

The induction potential was evaluated on activity level, and not primarily on mRNA level as suggested by the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**).

As PSMA-617 is not a CYP inhibitor, this is acceptable. However, one batch of hepatocytes from different donors, i.e. a mixture of hepatocytes from different donors, was used, although the guideline specifies that the induction results should be evaluated separately for each donor. To justify this deviation of the study protocol the applicant argues that, despite using a mixture of hepatocytes from different donors, the results of the positive controls indicate that assay sensitivity and performance were sufficient. Therefore, the assay should be able to characterize the induction potential towards CYP enzymes. It is noted that the guideline indicates induction results should be evaluated separately for each donor, because the response can vary between donors as can the cell adhesion and viability. In addition, the dose response can vary. Mixing results in a less constant situation per test situation, which may probably explain the high variability observed in the induction study. Nevertheless, although we consider the mixing of donors not an ideal test set up, it is agreed that the response of the positive controls is sufficiently high in this situation to accept it.

In vitro drug interaction studies with transporters showed that ^{175}Lu-PSMA-617 solution is not an inhibitor of P-gp, BCRP, BSEP, MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, OATP1B1, and OATP1B3. ^{175}Lu-PSMA-617 solution was found to be not a substrate of P-gp, BCRP, MATE1, MATE2-K, OCT2, OAT1, and OAT3. It was not investigated whether ^{175}Lu-PSMA-617 solution is a substrate of OATP1B and OATP1B3, but this is acceptable given primarily renal elimination of the drug.

Toxicology

Rats and minipigs were shown to exhibit little toxicity when dosed with the unlabelled solution containing ^{175}Lu-PSMA-617 and PSMA-617 in an approximately 1:1 ratio in single dose toxicity studies. This solution formulation corresponds to the therapeutic agent to be used in humans. These studies

provided an ample safety margin of about 150 and 400 in rats and minipigs, respectively. Within the rat study only one female animal of the high dose group revealed macroscopic and microscopic changes of the right kidney (single, pale area with unilateral M-nephroblastoma). This might be a spontaneous or incidental change but in view of the fact that the kidneys are a primary site of PSMA uptake and that ^{177}Lu-PSMA-617 is rapidly excreted through the kidneys, nephrotoxicity might be a serious adverse event in the clinical setting and should thus be carefully monitored. Prominent reactions within the minipig study were acute inflammation on the injection site with haemorrhage, crust, necrosis and thrombosis, mainly in the high dose groups.

The estimated exposure multiples of the single-dose toxicity studies (150 and 400 in rats and minipigs, respectively) and the repeat-dose toxicity study were based on the potential maximum human dose of 275 µg whereas the maximum theoretical concentration value (Cmax) in the in vitro secondary pharmacology study (Study 100053460-4) was calculated after a bolus injection of 200 µg. The 275 µg mass dose provided the most conservative estimate and resulted in a calculated safety margin of 132-fold. However, due to the different values used in both studies, the safety margin was recalculated using the 200 µg dose. This value resulted in a 94-fold safety margin which is considered sufficient.

Whereas the single dose toxicity studies were performed with the unlabelled solution, only PSMA-617 was used as a test item in the repeated dose toxicity study in rats. The rats were shown to exhibit little toxicity when dosed with the unlabelled chemical precursor PSMA-617. However, these data can only be regarded as supportive since PSMA-617 did not mimic the intended human formulation, no TK analysis was made and no recovery period was included in this study. This is considered acceptable since no comparative values were raised in the clinical setting and no toxicities could be developed during the single dose toxicity study in rats. Further, the absence of the pharmacological activity of the non-radioactive part makes the occurrence of delayed toxicity unlikely. This view is in line with the guideline on radiopharmaceuticals (EMA/CHMP/SWP/686140/2018) and thus agreed.

Unlabelled PSMA-617 was not mutagenic as it did not induce mutations in any of the five histidine-requiring strains of Salmonella typhimurium under the performed study conditions.

No carcinogenicity studies have been conducted with ^{177}Lu-PSMA-617 or the PSMA-617 precursor as they are not required for an anticancer radioactive agent.

Studies on reproductive and developmental toxicity have not been performed with ^{177}Lu-PSMA-617, the unlabelled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617 and are not required for an anticancer radioactive agent.

Considering the maximum radiation absorbed dose to the testes of 6.22 Gy ^{177}Lu-PSMA-617 has the potential to cause infertility in male patients. Respective statements concerning possible effects of ^{177}Lu-PSMA-617 on fertility and cautionary measures for man planning to father a child are included in the SmPC and PL as requested.

Conclusions on ERA

Lutetium PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, Lutetium is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

^{177}Lu vipivotide tetraxetan is PSMA-targeted radioligand therapy developed to treat metastatic castration-resistant prostate cancer. Its primary and secondary pharmacology has been well characterised in vitro and in vivo. The pharmacokinetic and toxicology program is also considered acceptable. No toxicological effects were observed in the safety pharmacology or single dose toxicity

studies in rats and minipigs administered a non-radioactive formulation containing unlabelled vipivotide tetraxetan and lutetium (^{175}Lu) vipivotide tetraxetan, or in repeat dose toxicity studies in rats administered unlabelled vipivotide tetraxetan. There are no objections to approval from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

This application is supported by a single prospective, open-label, multicenter, randomized Phase 3 study (PSMA-617-01 (VISION)) in patients with PSMA-positive mCRPC, comparing 177Lu-PSMA-617 in addition to best supportive care /best standard of care versus BSC/BSoC.

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

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 **Countries**: Belgium, Canada, Denmark, France, Germany, Netherlands, Sweden, United Kingdom, United States **Start**: 29-May-2018 **End**: 27-Jan-2021 (interim data cut-off)	Design, purpose & population: An international, prospective, open-label, multicenter, randomized, phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)	**Screening phase**: 1003 patients received ^{68}Ga-PSMA-11 **Age**: 40-94 (69.9) years **Groups:** 1 ^{68}Ga-PSMA-11 **Treatment phase:** 831 patients randomized to treatment with ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC alone **Age**: 40-94 (70.0) years **Groups**: 2 Group 1: 551	Form(s): ^{68}Ga-PSMA-11 (gallium (^{68}Ga) gozetotide) single i.v. injection Dosing information: 111-185 MBq (3-5 mCi) Imaging time: PET 50-100 min p.i. Form(s): ^{177}Lu-PSMA-617 (lutetium (^{177}Lu) vipivotide tetraxetan) i.v. administration Duration: 38 months: (treatment/ assessment period and long-term follow-up assessment) Doses: ^{177}Lu-PSMA-617 7.4 GBq (200 mCi) + Best standard of care for prostate cancer as defined by the investigator. Excluded: investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or	**Study Status**: ongoing, recruitment complete **Report no**. [PSMA-617-01] full, interim **Report date**: 28-Jun-2021 **Other reports**: **PK Report** [Study PSMA-617-01-Appendix 16.2.9.1] Report date: 16-Jun-2021 **DMPK Report** [Study PSMA-617-01-Appendix 16.2.9.2] Report date: 26-May-2021 **Cardiac Safety Report** [Study PSMA-617-01-Appendix 16.2.9.3] Report date: 09-Jun-2021 **Radiation Dosimetry Report for [177Lu]Lu-PSMA-617** [Study PSMA-617-01-Appendix 16.2.9.4] Report date: 10-May-2021

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
		Group 2: 280	hemi-body radiotherapy treatment. Best standard of care for prostate cancer as defined by the investigator.Excluded: investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment.	**Imaging Study Report:** PSMA-617-01 Imaging Study Report: Reviewer Variability Reviewer Variability Report date: 17-Jun-2021
Protocol: PSMA-617-02 **Countries**: United States **Start**: 05-Jul-2018 **End**: 15-Jan-2020	**Design, purpose & population**: PSMA-directed endoradiotherapy of castration-resistant prostate cancer (RESIST-PC). A **Phase 2 Clinical Trial**	**Total**: 71 (randomized), 64 (treated) **Age**: 54-95 (70.3) years (randomized patients) **Groups**: 2 Group 1: 23 Group 2: 41	**Form(s)**: ^{177}Lu-PSMA-617 i.v. administration, infused over approximately 15-30 minutes using an infusion pump **Duration**: 24 months (treatment/assessment and follow-up) **Doses**: ^{177}Lu-PSMA-617, 6.0 GBq ^{177}Lu-PSMA-617, 7.4 GBq	**Study Status**: Complete **Report no**. [PSMA-617-02], full final **Report date**: 07-Jan-2021 **Other reports**: None

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Within this Phase 3 study a dosimetry, pharmacokinetics and electrocardiogram sub-study also has been conducted in a subset of 30 patients during cycle 1 of the treatment. The patients continued in the sub-study as per the PSMA-617-01 protocol i.e. ^{177}Lu-PSMA-617 7.4 GBq dose every 6 (±1) weeks for a maximum of 6 cycles. Together with published literature, this supports the clinical pharmacology assessments of ^{177}Lu-PSMA-617 in patients with prostate cancer.

Because there were only 30 patients with pharmacokinetic data and also only 1 dose studied, no exposure-efficacy analysis were conducted and the exposure-safety analyses are for this reason considered only exploratory.

Methods

The high performance liquid chromatography with in-line radiodetection method to determine the possible presence of metabolites as a percentage of total radioactivity in each urine sample was not

validated in line with the recommendations in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

To evaluate whole body and organ radiation dosimetry of ^{177}Lu-PSMA-617, patients underwent full body (planar) and 3D SPECT/CT imaging during Cycle 1 of treatment. Baseline images were used to determine volumes in regions of interest (ROI/VOI) in selected major source organs such as the liver, spleen and kidneys. 3D SPECT/CT scans were also performed in the upper abdomen (comprising kidneys, liver and spleen). Kinetic data were modeled to determine normalized number of disintegrations. Normalized number of disintegrations were used with the RADAR/Medical Internal Radiation Dose (MIRD) method for internal dosimetry as implemented in the FDA cleared OLINDA (Organ Level Internal Dose Assessment) software to produce radiation exposure estimates. The human alimentary model, and urinary voiding bladder model (with a voiding interval of 3.5 h) as implemented in OLINDA were utilized.

Absorption

As ^{177}Lu-PSMA-617 is administered intravenously, bioavailability is 100%. No studies of bioavailability or effect of food were performed. No food effect is expected.

Bioequivalence

The proposed commercial formulation has small quantitative differences in excipients compared to the formulation used in Phase III clinical trial Study PSMA-617-01 which are considered minor and do not concern excipients that might influence the disposition of [^{177}Lu]Lu-PSMA-617 *in vivo*. Therefore, a comparative bioavailability study as per Bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, EMA 2010) is not required.

Distribution

Plasma protein binding as determined by ultrafiltration of unlabelled PSMA-617 and non-radioactive 175Lu-PSMA-617 at 1 and 5 µM was 58-70% and 62%-70%, respectively (study [0597]). Non-radioactive 175Lu-PSMA-617 and unlabelled PSMA-617 were both stable in for up to 2 hours at 37°C [Study 0594]. Hence, transchelation of lutetium from 175Lu-PSMA-617 to plasma proteins has not been observed.

The mean blood-to-plasma ratios for unlabelled PSMA-617 and non-radioactive 175Lu-PSMA-617 were 0.28 and 0.49, respectively (study [Q20_046]).

^{177}Lu-PSMA-617 was widely distributed to tissues and volume of distribution (Vz) was 123 L (78.1%).

The experimental data on biodistribution of ^{177}Lu-PSMA-617 were collected up to 156-168 h post injection, i.e. up to approximately one physical half-life of ^{177}Lu. This is comparable or higher than the measurement times used in other published studies with ^{177}Lu-PSMA-617. From the TACs shown in the Dosimetry report, it seems like at the last measurement time-point (ca. 160 hours post-injection) only a small amount of ^{177}Lu-PSMA-617 was still present in the body, hence the used measurement time is acceptable.

The source regions analysed within the sub-study of PSMA-617-01 are consistent with those considered in other published works on biodistribution and dosimetry of ^{177}Lu-PSMA-617.

Dosimetry

Tissue distribution was evaluated by dosimetry in 30 subjects with prostate cancer. The dosimetry of the sub-study PSMA-617-01 was done after one therapy cycle and extrapolated to other cycles (up to total administered activity of 44.4 GBq) assuming the same biokinetics. The absorbed organ doses were computed in the frame of the sub-study PSMA-617-01 using the software OLINDA/EXM version

2.2, based on TIACs in the source regions brain, heart wall, kidneys, lacrimal glands, liver, lungs, red marrow, salivary glands, spleen, thyroid and whole body. The TIACs in urinary bladder contents were not explicitly computed from the images. The applicant utilised the urinary bladder voiding model of the software OLINDA/EXM instead, assuming voiding intervals of 3.5 hours. For lacrimal glands dosimetry a sphere model of OLINDA/EXM was used, which computes a self-absorption dose only, assuming an organ mass of 0.7 g. On average, the organs receiving the largest absorbed doses were the lacrimal glands, salivary glands, colon/rectum, and kidneys. In patients with mild and moderate renal impairment the absorbed doses for kidneys was on average 1.7-fold higher compared to patients with normal renal function. Decrease in dosimetry was relatively slow from large intestine, kidneys, and salivary glands compared to the decrease in other tissues. Absorbed dose coefficients estimated by the applicant for lacrimal and salivary glands, kidneys, liver spleen and bone marrow are in line with the corresponding values reported in the literature (see below tables).

Table 2 Summary of absorbed dose coefficients [Gy/GBq] in organs at risk for ^{177}Lu-PSMA-617.

Study	No. of patients Activity per cycle	Imaging Modality	Lacrimal glands Mean±SD	Salivary glands Mean±SD	Kidneys Mean±SD	Liver Mean±SD	Spleen Mean±SD	Bone Marrow Mean±SD
Sub-study PSMA-617-01	29 pts 6.7-7.5 GBq	Planar, SPECT/CT	2.1 ± 0.47 (1.2-3.2)	0.63 ± 0.36 (0.22-1.5)	0.43 ± 0.16 (0.22-0.83)	0.090 ± 0.044 (0.043-0.22)	0.067 ± 0.027 (0.031-0.14)	0.035 ± 0.020 (0.020-0.13)
Yadav et al (2017)	26 pts 1.11-5.50 GBq	Planar (SPECT/CT for salivary gland volume only)	n.a.	1.244 ± 0.268	0.991 ± 0.312	0.3615 ± 0.108	n.a.	0.048 ± 0.059
Kratochwil et al (2016)	4 pts 6 GBq	Planar (single-abdominal SPECT/CT not used for dosimetry)	n.a.	1.48 ± 0.37 (SM) 1.28 ± 0.40 (PG)	0.75 ± 0.19	0.10 ± 0.03	0.19 ± 0.07	0.03±0.01
Kabasakal et al (2017)	7 pts 3.6-7.4 GBq	SPECT/CT	n.a.	1.90 ± 1.19 (PG)	0.82 ± 0.25	0.17 ± 0.09	n.a.	0.03±0.008
Delker et al (2016)	5 pts 3.4-3.9 GBq	SPECT/CT	n.a.	1.4 ± 0.53	0.6 ± 0.19 (Left) 0.61 ± 0.16 (Right)	0.11 ± 0.06	0.10 ± 0.03	0.012 ± 0.00524
Scarpa et al (2017)	10 pts 5.4 to 6.5 GBq	Planar (single abdominal SPECT/CT)	1.01±0.69	0.498 ± 0.15 (SM) 0.56 ± 0.25 (PG)	0.60±0.36	0.12±0.06	0.12±0.09	0.04±0.028
Maffey-Steffan et al (2020)	32 pts 6 GBq	Planar (single abdominal SPECT/CT)	0.85±0.51	0.46 ± 0.17 (SM) 0.53 ± 0.22 (PG)	0.77±0.56	0.13±0.08	0.13±0.16	0.039±0.028
Kamaldeep et al (2021)	30 pts	Planar (small ROI with no overlap to	1.45 ± 0.85	0.53 ± 0.30	0.52 ± 0.16	0.08 ± 0.05	0.17 ± 0.07	0.04 ± 0.03

Study	No. of patients Activity per cycle	Imaging Modality	Lacrimal glands Mean±SD	Salivary glands Mean±SD	Kidneys Mean±SD	Liver Mean±SD	Spleen Mean±SD	Bone Marrow Mean±SD
	4.44–5.55 GBq	avoid overestimation errors)						
Hohberg et al (2016)	9 pts 5.28–5.77 GBq	Planar (ROIs specifically drawn to avoid overlap)	2.82 ± 0.76	0.721 ± 0.142	0.525 ± 0.173	n.a.	n.a.	n.a.
Mix et al (2021)[1]	59 pts 6 GBq (Median)	SPECT/CT	n.a.	n.a.	0.67 ± 0.24	n.a.	n.a.	n.a.
Violet et al (2019)	30 pts 5.7–8.7 GBq	SPECT/CT	0.36 ± 0.18	0.44 ± 0.36 (SM) 0.58 ± 0.43 (PG)	0.39 ± 0.15	0.1 ± 0.05	0.08 ± 0.06	0.11 ± 0.10
Rosar et al (2021)[2]	24 pts 3–10.9 GBq	SPECT/CT	n.a.	0.72 ± 0.39 (SM) 0.81 ± 0.34 (PG)	0.54 ± 0.28	0.10 ± 0.05	n.a.	n.a.
Paganelli et al (2020)[3]	13 pts 3.7–5.5 GBq	Planar (single abdominal SPECT/CT)	2.26 (0.48-3.59)	0.59 (0.23-1.51) (SM) 0.65 (0.33-2.63) (PG)	0.42 (0.14-0.81)	0.13 (0.05-0.53)	n.a.	0.036 (0.023-0.067)
Prive et al (2021)[4]	10 pts 3 -6 GBq	SPECT/CT	n.a.	0.39 ± 0.17	0.49 ± 0.11	0.09 ± 0.01	n.a.	0.02 ± 0.00

SM = submandibular; PG = parotid gland.

[1] Based on the abstract only as full text was not available at the time of submission.

[2] Data using planar and single SPECT/CT not shown

[3] Dosimetry performed in 9 patients during cycle 1 and 4 patients during cycle 2; data represents the median values of the mean absorbed dose (range)

[4] Study conducted in hormone-sensitive, metastatic prostate cancer; Dosimetry was done for two cycles in each of the 10 patients, therefore the mean and SD are derived from 20 evaluations.

The dosimetry data including absorbed and effective doses is presented in the table below:

Table 3 Estimated absorbed dose for Pluvicto in the VISION sub-study

	Absorbed dose per unit activity (mGy/MBq)[a] (N=29)		***Calculated absorbed dose for 7 400 MBq administration (Gy)[a]***		***Calculated absorbed dose for 6 x 7 400 MBq (44 400 MBq cumulative activity) (Gy)[a]***	
Organ	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
Adrenals	*0.033*	*0.025*	*0.24*	*0.19*	*1.5*	*1.1*
Brain	*0.007*	*0.005*	*0.049*	*0.035*	*0.30*	*0.22*
Eyes	*0.022*	*0.024*	*0.16*	*0.18*	*0.99*	*1.1*

Gallbladder wall	*0.028*	*0.026*	*0.20*	*0.19*	*1.2*	*1.1*
Heart wall	*0.17*	*0.12*	*1.2*	*0.83*	*7.8*	*5.2*
Kidneys	*0.43*	*0.16*	*3.1*	*1.2*	*19*	*7.3*
Lacrimal glands	*2.1*	*0.47*	*15*	*3.4*	*92*	*21*
Left colon	*0.58*	*0.14*	*4.1*	*1.0*	*26*	*6.0*
Liver	*0.090*	*0.044*	*0.64*	*0.32*	*4.0*	*2.0*
Lungs	*0.11*	*0.11*	*0.76*	*0.81*	*4.7*	*4.9*
Oesophagus	*0.025*	*0.026*	*0.18*	*0.19*	*1.1*	*1.1*
Osteogenic cells	*0.036*	*0.028*	*0.26*	*0.21*	*1.6*	*1.3*
Pancreas	*0.027*	*0.026*	*0.19*	*0.19*	*1.2*	*1.1*
Prostate	*0.027*	*0.026*	*0.19*	*0.19*	*1.2*	*1.1*
Red marrow	*0.035*	*0.020*	*0.25*	*0.15*	*1.5*	*0.90*
Rectum	*0.56*	*0.14*	*4.0*	*1.1*	*25*	*6.2*
Right colon	*0.32*	*0.078*	*2.3*	*0.58*	*14*	*3.4*
Salivary glands	*0.63*	*0.36*	*4.5*	*2.6*	*28*	*16*
Small intestine	*0.071*	*0.031*	*0.50*	*0.23*	*3.1*	*1.4*
Spleen	*0.067*	*0.027*	*0.48*	*0.20*	*3.0*	*1.2*
Stomach wall	*0.025*	*0.026*	*0.18*	*0.19*	*1.1*	*1.1*
Testes	*0.023*	*0.025*	*0.16*	*0.18*	*1.0*	*1.1*
Thymus	*0.025*	*0.026*	*0.18*	*0.19*	*1.1*	*1.1*
Thyroid	*0.26*	*0.37*	*1.8*	*2.7*	*11*	*16*
Total body	*0.037*	*0.027*	*0.27*	*0.20*	*1.6*	*1.2*
Urinary bladder wall	*0.32*	*0.025*	*2.3*	*0.19*	*14*	*1.1*
Effective dose[b]	*0.120 mSv/MBq*	*0.043 mSv/MBq*	*0.886 Sv*	*0.315 Sv*	*5.319 Sv*	*1.892 Sv*

[a] *Absorbed dose estimates were derived using OLINDA v2.2. Values have been calculated based on dosimetry estimates at full precision and rounded to relevant digits.*

[b] *Derived according to ICRP Publication 103.*

Metabolism

Non-radioactive 175Lu-PSMA-617 and unlabelled PSMA-617 were both stable in for up to 2 hours at 37°C [Study 0594]. Additionally, non-radioactive 175Lu-PSMA-617 and unlabelled PSMA-617 were found to be metabolically stable against enzymatic degradation by liver and kidney human, rat, and minipig S9 fractions up to 1 hour at 37°C with enzyme cofactors [Study 0590] [Study 0591].

In vivo stability of ^{177}Lu-PSMA-617 was evaluated in urine samples of the 30 patients in the sub-study. Parent ^{177}Lu-PSMA-617 was the main compound detected in all samples: the relative concentration in the 0 to 2 hours urine collection ranged from 91% to 100% of the radioactivity and by 72 hours post-dose between 49% and 100% of the total radioactivity. Note that the total radioactivity at 72h post-dose was considerably lower than radioactivity during the first 24h. However, because the urine collections were not cumulative, no assessment of absolute [^{177}Lu]Lu-PSMA-617 concentration or recovery was performed.

Overall, these data indicate that ^{177}Lu-PSMA-617 is only metabolised to a minor extent.

Elimination

The applicant as well as other authors (Kratochwil et al. doi: 10.2967/jnumed.115.171397; Kabasakal et al. doi: 10.4274/mirt.08760) concluded that ^{177}Lu-PSMA-617 is excreted predominantly via kidney-urinary pathway. As reported by Kabasakal et al., more than half of the administered activity was eliminated through kidneys. Kratochwil et al. stated that approximately 50% of the administered activity was excreted by urine during the first 48 hours and that approximately 1-5% of the injected ^{177}Lu-PSMA-617 activity was eliminated by fecal excretion (it is not clear though for which time-period the gastro-intestinal excretion was reported).

In the sub-Study PSMA-617-01 the presence of [^{177}Lu]Lu-PSMA-617 was confirmed in all samples containing radioactivity. The most common metabolites were M1, M3, and M4, however no metabolite was excreted in urine in a significant amount up to 48 hours.

Dose proportionality and time dependencies

In Study PSMA-617-01, a dose of 7.4 GBq ^{177}Lu-PSMA-617 administered once every 6 weeks for a maximum of 6 cycles has been used, for a cumulative dose of 44.4 GBq.

A dose of 7.4 GBq is proposed for all subjects. However, dose reduction by 20% for ADRs are recommended in case of dry mouth Grade ≥3, renal toxicity or GI toxicity Grade ≥3).

PopPK Modelling

A popPK model was developed to characterise the radioactivity-blood PK of [^{177}Lu]Lu-PSMA-617 in a substudy of N=30 patients. Predicted exposure metrics were further used to investigate the correlation between exposure, dosimetry and toxicity.

The final model was a three-compartment model with a delayed 0-order absorption and linear elimination; parameter estimates from the final PopPK model are listed in the following table.

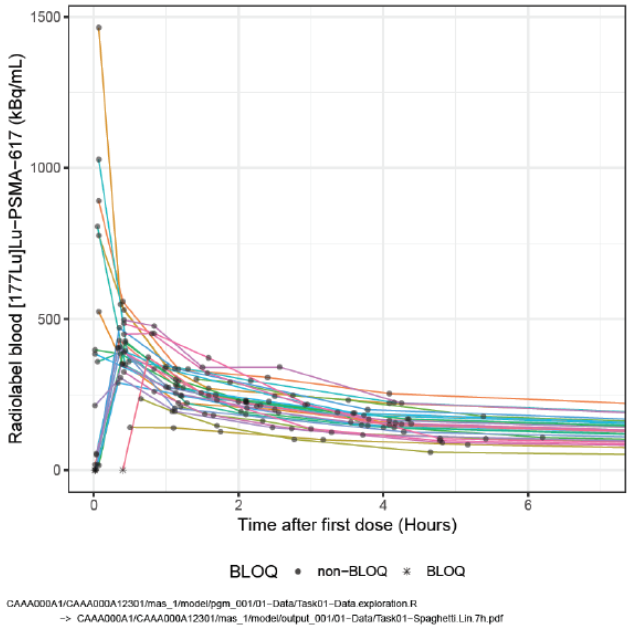
Table 4: Parameter estimates from the final PopPK model

Parameter (Unit)	Fixed effect			IIV			
	Estimate	SE	RSE (%)	CV (%)	Estimate (SD)	SE	RSE (%)
Tlag (h)	0.01	0.006	48	291	1.50	0.35	23
Tk0 (h)	0.06	0.03	54	264	1.44	0.36	25
Cl ($L.h^{-1}$)	2.50	0.11	4	22	0.22	0.03	14
$CrCl_{BL}$ effect on Cl	0.46	0,10	22	NA	NA	NA	NA
V_1 (L)	11.53	1.16	10	42	0.40	0.06	15
WT_{BL} effect on V_1	0.75	0.33	45	NA	NA	NA	NA
Q_2 ($L.h^{-1}$)	0.52	0.07	13	80	0.70	0.10	14
V_2 (L)	29.34	4.42	15	93	0.79	0.11	14
Q_3 ($L.h^{-1}$)	12.00	2.11	18	0	0 FIX	NA	NA
V_3 (L)	11.51	0.67	6	0	0 FIX	NA	NA
	Correlation parameters						
Correlation Cl/V_1	0.84	0.08	10	NA			
Correlation Q_2/V_2	0.86	0.05	6	NA			
	Residual error model parameter						
Proportional error (%)	13.96	1	7	NA			

$CrCl_{BL}$: baseline creatinine clearance; CV: coefficient of variation; IIV: inter-individual variability; NA: not applicable; RSE: relative standard error; SD: standard deviation; SE: standard error; WT_{BL}: baseline weight; 0 FIX: fixed variability to 0.
CV (%) was calculated using $\sqrt{e^{SD^2}-1}\cdot 100\%$.
SD corresponds to the estimated omega from Monolix. Covariates were normalized by the weighted mean value and log-transformed. The weighted mean for WT_{BL} and $CrCl_{BL}$, calculated by Monolix, were 88.5 kg and 101.5 mL/min, respectively.
Source: CAAA000A1/CAAA000A12301/mas_1/model/pgm_001/02-PopPK/Runs.Submission/Run16.mlxtran
Output: CAAA000A1/CAAA000A12301/mas_1/model/pgm_001/02-PopPK/Runs.Submission/Run16/populationParameters.txt

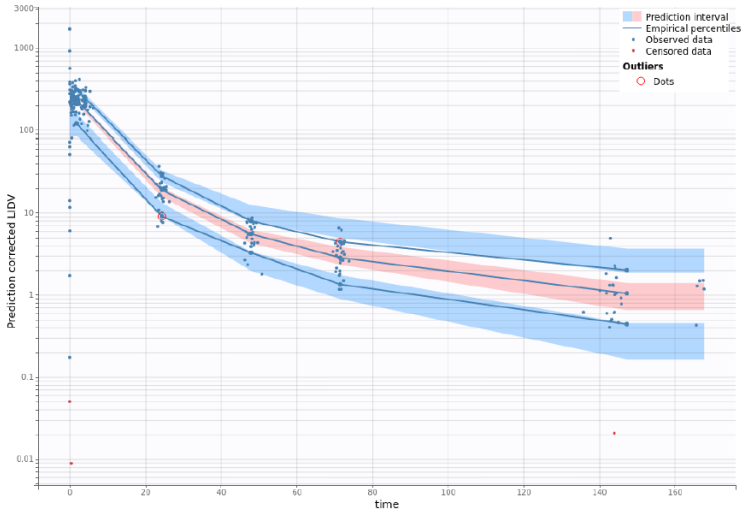
High unexplained variability was observed for Tlag (CV = 291%, RSE = 48 %, shrinkage 44%) and TK0 (CV = 264%, RSE = 54%, shrinkage 50%), which are used to describe an artificial delayed absorption after the start of administration. Apparent difficulties occurred to describe the absorption phase properly due to very high variability and low number of subjects. The broad range of infusion times (2 minutes to 1 hour 45 min) might be problematic for data analysis, even though no clear relationship between infusion duration and plasma concentration could be found. It was not evaluated whether different qualities of the used drug influenced radioactivity-drug PK.

In general, GOF plots demonstrated a reasonable agreement between data and model predictions. The residuals (IWRES and NPDE) were distributed symmetrical around the zero line. Early samples tended to have higher variability. pcVPCs showed an adequate predictive ability of the final popPK model during elimination phase (Figure 4).



The black dots correspond to the observations above the LOQ, and black crosses to the observations below the LOQ. The lines are colored by subjects.
BLOQ: below the limit of quantification.

Figure 3: Spaghetti plots of observed individual radioactivity-blood PK of Lu-PSMA-617 limited to the first 7 hours



The time corresponds to the time after start of infusion, in hours. LIDV corresponds to the concentration in kBq/mL. Solid lines display observed 10th, 50th, 90th percentiles. Blue/Pink regions show 90% prediction interval around the percentiles. Blue dots are the concentrations above the LOQ and red dots the simulated concentrations below the LOQ.
Source: CAAA000A1/CAAA000A12301/mas_1/model/pgm_001/02-PopPK/Runs.Submission/Run16/ChartsFigures/vpc_LIDV_0_0.png

Figure 4: VPC from the final popPK model

Weight, BMI, age and baseline CrCL were investigated as covariates. Baseline CrCL had a significant impact on CL and weight had a significant impact on V1. No requirements for dose adjustments were derived by the Applicant from these results. In popPK modelling baseline CrCL was found as a significant covariate on CL as described under 2.1.2.

Based on simulations using the popPK model, renal impairment resulted in 20% increased AUCinf for mild renal impairment and 42% increased AUCinf for moderate renal impairment. The underlying population (N=30) included only 1 patient with moderate renal impairment and 10 patients with mild renal impairment, no patients with severe renal impairment were included. Renal impairment showed a

non-significant trend toward higher kidney dosimetry values and higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline CrCL. Adjusted dosing for patients with renal impairment was not proposed, instead a new PBPK model was used to predict exposure in patients with renal impairment. Kidney dose at cycle 6 was increased more than twofold in patients with moderate renal impairment and 1,7-fold in patient with mild renal impairment according to the VISON study and the proposed PBPK model.

Estimated AUCinf and Cmax were further used for E-R analyses, more specifically for exposure-dosimetry and exposure-dosimetry-toxicity analyses.

The exposure-dosimetry analysis was limited by the small sample size (N=29). For Cycle 1 no consistent trend was shown between injected activity and AUCinf or Cmax. The AUCinf effect on kidney dosimetry, might be confounded by CrCLBL, as it has both an effect on AUCinf and on kidney dosimetry.

Exposure/Dosimetry-Toxicity analyses are limited by small sample size, the small number of adverse events and the fact that only data from treatment cycle 1 was used for the analysis. Descriptive plots showed a decrease in leukocytes, neutrophils and platelets after treatment administration. No statement regarding the risk of cumulative doses can be drawn from this analysis.

Special populations

The applicant has not conducted a dedicated renal impairment study for ^{177}Lu-PSMA-617. A correlation between a mild to moderate renal impairment in patients treated with ^{177}Lu-PSMA-617 and the corresponded absorbed doses to kidneys was analysed though.

PopPK modelling baseline CrCL was found as a significant covariate on CL. Based on simulations, renal impairment resulted in 20% increased AUCinf in mildly renally impaired patients and 42 % increased AUCinf in moderately renally impaired patients. The underlying population (N=30) included only 1 patient with moderate renal impairment and 10 patients with mild renal impairment, no patients with severe renal impairment were included.

In addition to that, renal impairment showed a non-significant trend toward higher kidney dosimetry values and higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline CrCL.

No dedicated study in patients with liver impairment has been conducted. As ^{177}Lu-PSMA-617 is not metabolized by, or primarily eliminated through, the liver, PK and biodistribution are not affected by hepatic impairment. Hence, the applicant proposed no dose adjustment in patients with hepatic impairment.

Age, in the range of 52 to 80 years (median 67 years) in the PSMA-617-01 sub-study, was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model and therefore, the applicant recommends no dose adjustment in patients aged 65 years or older in the proposed product information.

Table 5: Summary of PK metrics per age group in cycle 1

Parameter	Age	n	Min	Median	Max	CV%
AUCinf (MBq.h/L)	< 65	11	1413.54	2648.62	3059.66	18.56
	65-74	15	1734.33	2895.16	4796.19	27.12
	75-80	3	3526.17	3963.34	5340.67	22.14
Cmax (kBq/mL)	< 65	11	205.26	556.58	761.91	30.16
	65-74	15	302.09	596.71	1092.24	36.41
	75-80	3	565.42	658.83	893.55	23.95

Pharmacokinetic interaction studies

The results from in vitro CYP450 induction and inhibition studies indicate that ^{177}Lu-PSMA-617 is neither an inducer nor an inhibitor of the investigated CYP450 enzymes and at the investigated range of concentrations, respectively.

^{177}Lu-PSMA-617 is metabolically stable both in in vitro and in vivo and is assumed to be passively cleared renally, however PSMA-11 rather than 175Lu-PSMA-617 was used in the in vitro studies with uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp and BCRP).

Androgen deprivation therapy and other therapies targeting the androgen pathway, such as androgen receptor antagonists, have been reported to modulate PSMA expression in some nonclinical prostate cancer models, and in some clinical studies (Afshar-Oromieh et al 2018, Emmett et al 2019, Vaz et al 2020, Mathy et al 2021) and might in this way affect the efficacy of ^{177}Lu-PSMA-617. Only patients with confirmed PSMA expression were included in the study and subgroup analysis were conducted for comedication with androgen axis drugs which did not indicate that co-administration of androgen axis drugs had a detrimental effect.

2.6.2.2. Pharmacodynamics

Mechanism of action

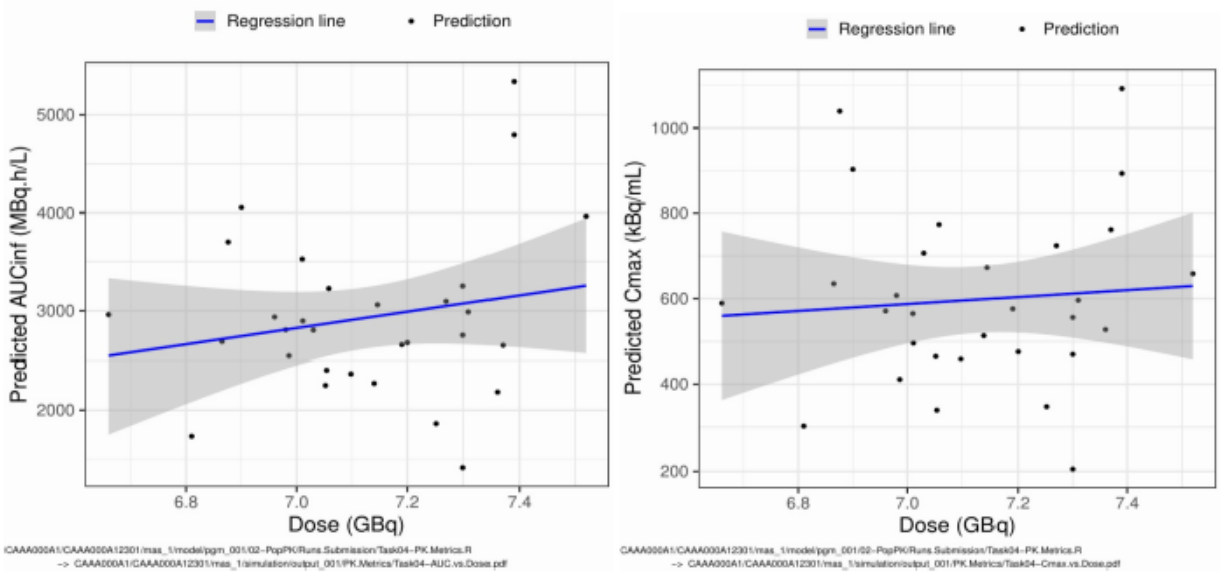
^{177}Lu-PSMA-617 is a PSMA-targeted radioligand therapeutic that delivers radiation to cancer cells via binding to the PSMA cell-surface target. Specifically, this agent has been designed to bind with high affinity to PSMA expressed on the surface of prostate cancer cells in order to target therapeutic radiation to sites of disease. The targeting and binding of the agent to PSMA occurs through the glutamate-urea-lysine pharmacophore portion of the molecule. In vitro experiments showed PSMA binding affinity to be high with nanomolar affinity reported in cellular assays. PSMA-dependent uptake and internalization of ^{177}Lu-PSMA-617, were also confirmed in cellular assays that lead to prolonged retention in the targeted cancer cell. The resulting radiation exposure causes DNA damage in these targeted cancer cells, as well as in neighbouring cells due to bystander and cross-fire effects, from the release of medium-energy β-particles emitted from Lu-177.

Primary and Secondary pharmacology

No dedicated PD studies have been submitted. No relevant pharmacodynamic effects related to the ligand itself are expected, as the total peptide mass of PSMA-617 ligand that is injected is low (with a potential maximum of 275 µg of total peptide), it is administered infrequently (every 6 weeks), and nonclinical studies demonstrated a lack of direct pharmacological and toxicological effects across in vitro and in vivo assays at much higher exposures (see Non-clinical section).

Exposure-dosimetry analyses

Individual predicted AUCinf and Cmax derived from PopPK modelling were plotted against injected dose and did not show any clear trend of correlation, as illustrated in below figure.



The blue lines are the regression lines with the 95% confidence intervals in grey.

Figure 5: Predicted AUCinf and Cmax vs. injected dose

Effect of exposure on dosimetry in critical organs (i.e. kidney, bone marrow, salivary glands and lacrimal glands) during the first cycle of treatment in mCRPC patients were explored. Dosimetry assessments for each organ of interest were available in 29 patients from the PSMA-617-01 sub-study.

Table below summarizes the dosimetry values (in Gy) calculated on Cycle 1 per organs. The highest dosimetry values were observed in lacrimal glands. Lower dosimetry values were observed in salivary, kidney, and bone. One patient had a very high bone marrow dosimetry compared to the others.

Table 6: Summary of dosimetry values (Gy) per organs on Cycle 1

Organ	Min	1st quartile	Median	Mean	3rd quartile	Max	SD	CV%
Bone marrow	0.14	0.18	0.21	0.25	0.27	1.00	0.15	62
Kidney	1.57	2.13	2.72	3.10	3.93	6.03	1.22	39
Lacrimal glands	8.15	12.81	14.67	14.75	16.87	22.02	3.43	23
Salivary glands	1.52	2.44	3.78	4.47	5.83	10.76	2.61	58

CV%: coefficient of variation calculated as SD/Mean*100%.
Source: CAAA000A1/pk/pk_1/pgm/pkpd/Task01-PK-Dosimetry.R
Output: CAAA000A1/pk/pk_1/reports/pkpd/Task01-Summary.dosimetry.csv

The relationship between exposure and dosimetry from organs at risk at Cycle 1 were explored. The strongest correlation was observed between blood AUCinf and kidney dosimetry (R=0.51). The Pearson correlation coefficients also suggested some degrees of correlation between blood AUCinf and dosimetry in bone marrow (R=0.36) and in lacrimal glands (R=0.28), between Cmax and kidney dosimetry (R=0.31), as well as between injected activity and dosimetry in bone marrow (R=0.32) and in kidney (R=0.3). Linear regression was performed for each exposure-dosimetry relationship, and results show that AUCinf in blood is a statistically significant predictor of kidney dosimetry (p=0.005). Results from the linear regression between AUCinf and kidney dosimetry are reported in below table. This analysis suggests that an increase in AUCinf by 1000 MBq.h/L would lead to an increase in kidney dosimetry by 0.7 Gy.

Table 7: Results from the linear regressions between AUCinf and kidney dosimetry

Parameter	Estimate	95% CI	p-value
Intercept	0.95	[-0.55 – 2.45]	0.20
AUCinf effect	0.0007	[0.0002 – 0.0012]	0.005*

*Significant p-value (p<0.05). CI: confidence interval.

Exposure/dosimetry-toxicity analyses

Relationships between exposure/dosimetry and acute toxicity related to kidney, bone marrow, salivary and lacrimal glands during the first cycle of treatment with [^{177}Lu]Lu-PSMA-617 in mCRPC patients were explored. Due to the limited number of patients (N=30) and adverse events, only descriptive plots were generated.

CrCL, as a surrogate of renal function, and renal adverse events were explored to evaluate the risk related to kidneys. Hemoglobin, leukocyte, neutrophil and platelet counts together with their associated adverse events (i.e. anemia, leukopenia, neutropenia and thrombocytopenia) were explored as indicators for hematological toxicity.

In the PK/Dosimetry-Toxicity datasets, occurrence of toxicity and their associated grades were considered as categorical variables and laboratory values as continuous variables. All the exposure metrics were considered as continuous variables.

Longitudinal laboratory data during Cycle 1 were first explored from a total of 30 patients, the majority of the individuals had one baseline and 5 post-baseline observations available. Only few individuals reached the threshold for hematological adverse event of CTCAE Grade $\geq$ 2 related to hemoglobin, leukocytes, neutrophils or platelets. Those patients were the ones with low baseline levels for the associated laboratory values.

First, exposure/dosimetry-toxicity analyses explored the worst decrease from baseline in CrCL, reflecting renal function, and the worst decrease from baseline in platelet count, the most radiation-sensitive hematological laboratory assessment. Among the sub-study patients with post-baseline assessments, 17 (59%) showed a decrease from baseline in CrCL and 25 (86%) experienced a decrease in platelet count during Cycle 1.

The worst individual CrCL decrease (% change from baseline) at Cycle 1 was plotted against each exposure metrics for each one of the 17 patients who had a decrease in CrCL from baseline. Higher injected activity and higher kidney dosimetry tend to be associated with larger decrease in CrCL change from baseline. The positive trend between worst CrCL decrease and exposure in blood (AUCinf and Cmax) may be due to the limited sample size, the variability in the data and the presence of outliers.

No clear and consistent trend could be detected between worst platelet count decrease or haematological toxicity grades/adverse events and exposure.

Also, for patients experiencing at least one salivary gland toxicity (any grade), no consistent trend across the four exposure metrics was observed.

PK/QT analysis

For clinical cardiodynamic evaluation compliant with ICH E14, ECGs and time-matched PK were collected in the sub-study for PSMA-617-01. ECGs and PK samples were collected prior to administration and at 1, 4, and 24 hours post-dose. The primary objective was to evaluate the effect of

^{177}Lu-PSMA-617 on the QTc interval using the Fridericia method (QTcF) using a by-timepoint analysis as the primary analysis and concentration-QTc effect analysis as a secondary analysis.

In the by-timepoint analysis (N=30), ^{177}Lu-PSMA-617 had no clinically relevant effect on QTcF, with the QTcF change-from-baseline ranging from -5.2 ms to 2.1 ms. The concentration-QTc analysis was confirmatory, with a model predicted QT change from baseline (ΔQTcF) of 3.1 ms (2-sided 90% upper confidence bound 5.5 ms) at geometric mean Cmax 3.8 ng/mL. Based on the concentration-QTc analysis, an effect on ΔQTcF exceeding 20 ms can be excluded within the full observed range of ^{177}Lu-PSMA-617 plasma concentrations and up to ~6 ng/mL.

2.6.3. Discussion on clinical pharmacology

A sub-study within pivotal Phase 3 study PSMA-617-01 evaluated dosimetry in 29 patients, and PK and ECG in 30 patients from a non-randomized cohort receiving ^{177}Lu-PSMA-617+BSC/BSoC. The supportive pharmacokinetic and biodistribution/dosimetry information collected from the available literature provides a background information for this application.

Methods

The high-performance liquid chromatography with in-line radiodetection method to determine the possible presence of metabolites as a percentage of total radioactivity in each sample was not validated in line with the recommendations in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). Since the purpose was exploratory and a relative quantitation rather than an absolute quantitation of concentration of [^{177}Lu]Lu-PSMA-617 and metabolites was the objective, the method is considered fit for that purpose.

Distribution

Tissue dosimetry distribution was in general similar for ^{177}Lu-PSMA-617 and Ga-PSMA-11 except for dosimetry in large intestine, which appears higher for ^{177}Lu-PSMA-617 compared to Ga-PSMA-11. Since the PSMA-targeting pharmacophore glutamate-urea-lysine is the same in both substances a similar tissue distribution is expected. The applicant discussed that the apparent difference in tissue dosimetry between ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11 could be due to the difference in effective half-lifes of ^{177}Lu and ^{68}Ga, 33h vs 54 min, respectively. Indeed effective half-life of ^{68}Ga is so short that no activity could be detected by the time that ^{68}Ga-PSMA-11 could have reached the large intestine if part of the dose would be excreted in the faeces.

Dosimetry

The proposed treatment regime (7.4 GBq pro cycle administered every 6 weeks (± 1 week) over a maximum of 6 cycles) was selected with the purpose of delivering the highest possible dose to the tumour and simultaneously without causing serious toxicity in the patient. The absorbed doses in organs at risk need to be carefully considered while prescribing treatment regimens to individual patients.

The applicant provided additional data comprising of the results of the dosimetric calculations conducted in the frame of an ongoing clinical study with ^{177}Lu-PSMA-617. Overall, the comparison of the cumulative absorbed doses in organs at risk computed (partly) based on the data from the individual therapy cycles and extrapolated from the data in cycle 1 showed that, at least in the considered patient population, the extrapolation method overestimated the cumulative absorbed doses in all organs at risk except the salivary glands. This is not expected to be a major issue from the safety point of view, since it gives a conservative estimation of the absorbed organ doses. Nonetheless, it is

not ideal for the treatment optimisation based on the maximum tolerable absorbed dose in non-target organs or tissues, as less activity will be administered than actually tolerable.

The urinary bladder voiding model of the software OLINDA/EXM with voiding intervals of 3.5 hours was employed by the applicant for dosimetry. It is not clear which assumptions regarding the voiding fractions and the biological half-lives were made. The source region "generalised GI" showed the highest uptake of ^{177}Lu-PSMA-617, however TIACs for this region are not given. It is stated in the dosimetry report that human alimentary tract model as implemented in OLINDA/EXM was utilised. Here it was not clear either which specific assumptions were made. The applicant recapitulated literature findings regarding the excretion of ^{177}Lu-PSMA-617. Only one study by Kratochwil et al. reported quantitative data on the elimination of ^{177}Lu-PSMA-617 by faecal excretion (1-5 %). From this study it is not clear though for which time-period the abovementioned gastro-intestinal excretion was evaluated. The applicant also suggested that the relatively low absorbed dose to liver was an indication of only a minor excretion of ^{177}Lu-PSMA-617 via liver. The applicant further argued that a higher absorbed dose would be expected, were the excretion via liver more considerable. This argument is not appropriate though, since an uptake in a specific organ affects the corresponding absorbed dose and not the other way around.

Even though only limited quantitative data assessing the excretion of ^{177}Lu-PSMA-617 via alimentary tract are available, it seems to be consistent among several studies that the alimentary tract plays only a minor role in the elimination of ^{177}Lu-PSMA-617. The applicant concluded that ≥ 80% of ^{177}Lu-PSMA-617 is excreted via the kidney-urinary pathway. It is agreed that excretion in urine in the major elimination pathway, but urinary excretion was <80% after 2 days and excretion in the faeces of 1-5% seems only be based on data within 2 days after administration, which is too short to conclude absence of excretion in the faeces. Further, diarrhoea occurred more often for ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm. Therefore, it cannot be excluded that a somewhat greater part than 1-5% of the administered ^{177}Lu-PSMA-617 is excreted in the faeces and that the apparent difference in tissue dosimetry between ^{177}Lu-PSMA-617 and ^{68}Ga-PSMA-11 is partly due to differences in effective half-life of ^{177}Lu and ^{68}Ga and resulting different local exposure-time profiles of these moieties in the large intestine.

The applicant highlighted possible uncertainties in the computed doses for such small organs as lacrimal glands, due to substantial uncertainties of the planar based image quantification for these regions.

Absorbed dose coefficients estimated by the applicant for lacrimal and salivary glands, kidneys, liver spleen and bone marrow are in line with the corresponding values reported in the literature.

Based on the analyses done by the applicant to investigate the correlation between the kidney function of patients treated with ^{177}Lu-PSMA-617 and the absorbed dose to kidneys, it seems that mild to moderate renal impairment affects the absorbed dose to kidneys. The clinical relevance of this finding is difficult to interpret as there is no clear relationship established between kidney dosimetry and clinical safety. The computed absorbed dose to kidneys for a patient with a moderate renal impairment lied within the distribution observed for patients with mild renal impairment. The applicant concluded that mild and moderate renal impairment are unlikely to warrant any adjustments in administered activities, since no clinically significant renal toxicity was observed in the study PSMA-617-01 in spite of higher doses to the kidneys. However, no information is available for severe renal impairment or end-stage renal disease, for which kidney doses are expected to be even higher. Therefore, the treatment with Pluvicto is not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end stage renal disease. This has been reflected in the PI.

<u>Excretion</u>

^{177}Lu-PSMA-617 is likely to be eliminated mainly by excretion in the urine. Because of the high dosimetry in the large intestine excretion in the faces cannot be excluded. Determination of the presence of metabolites in urine samples indicated that ^{177}Lu-PSMA-617 was the main component present in urine indeed indicating importance of the renal excretion of ^{177}Lu-PSMA-617. Excretion, however, has not been quantified because no cumulative urine had been collected. Based on radioactivity remaining in the body a rough indication for the excretion can be obtained: after 2h, 22h, 45h, and 165h, 86%, 29%, 19%, and 7.5%, respectively, remained in the body. Hence, approximately 70% of the radioactivity was excreted within the first day followed by a slower elimination. Based on the high excretion during the first day, ^{177}Lu-PSMA-617 is probably mainly excreted in the urine.

A simple first order kinetics model was developed to describe the injected activity (IA) for kidney in the first cycle. The effect of renal function on the elimination, kidney dosimetry half-life and excretion half-life (hour) of the IA was approximately 40% and 25%, respectively, with increased half-lives in subjects with mild renal impairment. Renal function and adverse reactions should be frequently monitored in patients with mild to moderate renal impairment because of increased chance of AEs (see section 4.4). The text in section 5.2 special populations – renal impairment is aligned with the text in section 4.4.

Further, it is assumed that ^{177}Lu-PSMA-617 is excreted in urine via glomular filtration and that no active excretion is involved. The reabsorption of [^{177}Lu]Lu-PSMA-617 is unlikely because plasma clearance is in the range of a passive renal clearance. Further, amino acid infusion, which could reduce re-uptake in the kidneys, had no effect on the clearance of [^{177}Lu]Lu-PSMA-617, also indicating no or limited reabsorption in the tubuli.

popPK

A popPK model was developed to characterise the radioactivity-blood PK of [^{177}Lu]Lu-PSMA-617 in a substudy of N=30 patients. Predicted exposure metrics were used to investigate the correlation between exposure, dosimetry and toxicity.

Estimated AUCinf was further used for E-R analyses, more specifically for exposure-dosimetry and exposure-dosimetry-toxicity analyses.

The final popPK model was a three-compartment model with a delayed 0-order absorption and linear elimination. High unexplained variability was observed for Tlag (CV = 291%, RSE = 48 %, shrinkage 44%) and TK0 (CV = 264%, RSE = 54%, shrinkage 50%), which are used to describe an artificial delayed absorption after the start of administration. Apparent difficulties occurred to describe the absorption phase properly due to very high variability and low number of subjects. The broad range of infusion times (2 minutes to 1 hour 45 min) might be problematic for data analysis, even though no clear relationship between infusion duration and plasma concentration could be found. It was not evaluated whether different qualities of the used drug influenced results for radioactivity-drug PK.

As covariates were investigated weight, BMI, age and baseline CrCL. Baseline CrCL had a significant impact on CL and weight had a significant impact on V1. No requirements for dose adjustments were derived from these results.

The small sample size of N=30 patients sampled only in cycle 1 is regarded as limited data for population PK analysis. It is strongly recommended to update the popPK model with more PK data when possible, especially to provide more insight on the high variability. In addition, exposure-toxicity analyses could gain from data later treatment cycles, because more adverse events might occur in later treatment cycles.

In general, GOF plots demonstrated a reasonable agreement between data and model predictions. The residuals (IWRES and NPDE) were distributed symmetrical around the zero line. Early samples tended

to have higher variability. pcVPCs showed an adequate predictive ability of the final popPK model during elimination phase.

The applicant reported an effective half-time of ^{177}Lu-PSMA-617 in blood of ~ 33 hours in 29 patients. and clarified that the effective half-life of ^{177}Lu-PSMA-617 was not calculated individually for each patient, rather the geometric mean of the terminal elimination half-life was computed from the values assessed individually for 29 patients and utilised for the subsequent calculation of the effective half-life of ^{177}Lu-PSMA-617.

The applicant was recommended to update the popPK model with more PK data when possible, especially to provide more insight on the high variability. In addition, exposure-toxicity analyses could benefit from data on later treatment cycles, because more adverse events might occur in later treatment cycles.

Renal impairment

The applicant has not conducted a dedicated renal impairment study for ^{177}Lu-PSMA-617.

In popPK modelling baseline CrCL was found as a significant covariate on CL. Based on simulations, renal impairment resulted in 20% increased AUCinf in mildly renally impaired patients and 42 % increased AUCinf in moderately renally impaired patients. The underlying population (N=30) included only 1 patient with moderate renal impairment and 10 patients with mild renal impairment, no patients with severe renal impairment were included. Since there was only 1 subject with moderate renal impairment i.e. CrCL 54 ml/min in the pharmacology sub-study, these data should be interpreted cautiously. In addition, kidney dosimetry was on average 1.7-fold higher in subjects with mild renal impairment.

Further, renal impairment showed a non-significant trend toward higher kidney dosimetry values and higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline CrCL.

It is unlikely though that accumulation occurs with repeated dosing in patients with renal impairment given the estimated effective elimination half-life of 33h accounting for the decay of Lu-177 radioactivity in subjects with normal renal function and the dosing interval of 6 weeks; however, patients with renal impairment had more AEs (see safety) likely due to the higher prolonged exposure.

In study PSMA-617-01, renal function CrCL >50 ml/min was an inclusion criterion. Further, in the SmPC (Table 1 section 4.2) it is recommended to withhold treatment in patients with CrCL<30 ml/min. Therefore, treatment with ^{177}Lu-PSMA-617 cannot be recommended in patients with moderate and severe renal impairment with CrCL <50 ml/min. SmPC sections 4.2 and 4.4

The Applicant proposed revisions to the dedicated sections of the SmPC concerning patients with renal impairment. Following these amendments, the treatment with Pluvicto is currently not recommended in patients with moderate to severe renal impairment with baseline CLcr <50 mL/min or end stage renal disease. The Post Marketing Requirement from FDA, the Renal Impairment Study CAAA617A12202 (CSR expected to be available in Q4 2026) is set to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of ^{177}Lu-PSMA-617 and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment. It is expected that the study will provide additional information in this patient population with subsequent optimisation the labelling recommendations.

To improve the elimination the renal toxicity W&P within section 4.4 of the proposed EU SmPC advises on encouraged hydration/increasing of oral fluids and frequent voiding/urination.

Since ^{177}Lu-PSMA-617 is eliminated in the urine, guidance for subjects with urine incontinence is provided for patients and their care givers #in the PIL (see SmPC).

Hepatic impairment

No dedicated hepatic impairment study for ^{177}Lu-PSMA-617 has been conducted.

For hepatic impairment the inclusion criteria in the pivotal study were AST/ALT < 3 ULN or <5 ULN for patients with liver metastases and total bilirubin < 1.5 ULN. Further, in the SmPC it is recommended to discontinue treatment when AST/ALT are increased > 5 ULN. Therefore, there is very limited safety data in patients with hepatic impairment. It is however agreed that varying degrees of hepatic impairment are not likely to affect the pharmacokinetics of [^{177}Lu]-PSMA-617 since it is not metabolised. Also hepatotoxicity was not remarkable in VISION. However, there is no experience with patients with moderate and severe hepatic impairment and this is reflected in the SmPC section 4.2.

Special populations

Since ^{177}Lu-PSMA-617 has been limited to investigations in prostate cancer, exclusive to males, there is no information regarding the impact of gender on PK or biodistribution. ^{177}Lu-PSMA-617 is not indicated for use in females.

Although currently no information is available about the effects of race or ethnicity, the effect by ethnic factors on PK is considered unlikely.

Age, in the range of 52 to 80 years (median 67 years) in the PSMA-617-01 sub-study, was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model. However, higher absorbed radiation dose levels in the kidneys and bone marrow had been observed in older patients, despite the possibility that this correlation may be confounded by the negative correlation between age and renal clearance. Data provided during the procedure showed that the AUC in patients 75-80 years old is 1.5-fold higher compared to patients <65 years old (Median 3963.34 vs. 2648.62 MBq.h/L). Further clarification may be expected from the results of the planned Renal Impairment Study (Study CAAA617A12202) that the applicant was recommended to provide.

Drug drug interactions

^{177}Lu-PSMA-617 is metabolically stable both in in vitro and in vivo and is assumed to be passively cleared renally, however PSMA-11 rather than 175Lu-PSMA-617 was used in the in vitro studies with uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp and BCRP). The in vitro studies were not optimally reported and conducted.

Pharmacodynamics

^{177}Lu-PSMA-617 is a PSMA-targeted radioligand therapeutic that delivers radiation to cancer cells via binding to the PSMA cell-surface target. Specifically, this agent has been designed to bind with high affinity to PSMA expressed on the surface of prostate cancer cells in order to target therapeutic radiation to sites of disease.

The exposure-dosimetry analysis was limited by the small sample size (N=29). For Cycle 1 no consistent trend was shown between injected activity and AUCinf or Cmax. The AUCinf effect on kidney dosimetry, might be confounded by CrCLBL, as it has both an effect on AUCinf and on kidney dosimetry.

Exposure/Dosimetry-Toxicity analyses are limited by the small sample size, the small number of adverse events and the fact that only data from treatment cycle 1 was used for the analysis. Descriptive plots showed a decrease in leukocytes, neutrophils and platelets after treatment administration. No statement regarding the risk of cumulative doses can be drawn from this analysis.

According to the results of the PK/QT analysis together with the preclinical cardiac safety studies, there appears to be a negligible risk of an electrophysiological effect by 175Lu-PSMA-617. However, due to lack of a dedicated QT/QTC study and to the lack of systematic collection of ECGs during the pivotal study the risk for QT prolongation is not well characterized. Therefore, the Applicant is recommended to repeat the PK/QT assessment in the above-mentioned Renal Impairment Study (Study CAAA617A12202) performed in mCRPC patients (PAM-REC). ECGs and time-matched PK samples will be collected in all patients enrolled in all groups of the study (normal renal function, moderate and severe renal impaired patients) to enable concentration-QTc effect analysis on this data. The PK/QT assessment in Study CAAA617A12202 will be performed according to the Guideline CHMP/ICH/2/04.

2.6.4. Conclusions on clinical pharmacology

The applicant conducted a sub-study (within pivotal Study PSMA-617-01) to evaluate dosimetry, PK, ECGs, safety and tolerability, and urinary metabolic stability in a single-arm non-randomized cohort of 30 patients. The clinical pharmacology of ^{177}Lu-PSMA-617, well described in the literature, provides a background information for this application.

Overall, all aspects of the Clinical Pharmacology were sufficiently addressed. The Applicant was recommended to submit the results of the planned Renal Impairment Study (Study CAAA617A12202).

2.6.5. Clinical efficacy

The clinical data package is based on the results of the pivotal VISION Study (PSMA-617-01) and supportive RESIST-PC Study (PSMA-617-02).

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

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

The following Table 12 provides an overview regarding key factors of the pivotal trial PSMA-617-01 (and the safety-only-supportive trial PSMA-617-02):

Table 8: Overview of the pivotal trial PSMA-617-01 and supportive regarding safety only trial PSMA-617-02

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 **Countries**: Belgium, Canada, Denmark, France,	Design, purpose & population: An international, prospective, open-label, multicenter, randomized, phase 3 study of ^{177}Lu-	**Screening phase**: 1003 patients received ^{68}Ga-PSMA-11 **Age**: 40-94 (69.9) years **Groups:** 1	Form(s): ^{68}Ga-PSMA-11 (gallium (^{68}Ga) gozetotide) single i.v. injection Dosing information:	**Study Status**: ongoing, recruitment complete **Report no**. [PSMA-617-01] full, interim

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
Germany, Netherlands, Sweden, United Kingdom, United States **Start**: 29-May-2018 **End**: 27-Jan-2021 (interim data cut-off)	PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castrationresistant prostate cancer (mCRPC)	^{68}Ga-PSMA-11 **Treatment phase:** 831 patients randomized to treatment with ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC alone **Age**: 40-94 (70.0) years **Groups**: 2 Group 1: 551 Group 2: 280	111-185 MBq (3-5 mCi) Imaging time: PET 50-100 min p.i. Form(s): ^{177}Lu-PSMA-617 (lutetium (^{177}Lu) vipivotide tetraxetan) i.v. administration Duration: 38 months: (treatment/ assessment period and long-term follow-up assessment) Doses: ^{177}Lu-PSMA-617 7.4 GBq (200 mCi) + Best standard of care for prostate cancer as defined by the investigator. Excluded: investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment Best standard of care for prostate cancer as defined by the investigator. Excluded: investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment	**Report date**: 28-Jun-2021 **Other reports**: **PK Report** [Study PSMA-617-01-Appendix 16.2.9.1] Report date: 16-Jun-2021 **DMPK Report** [Study PSMA-617-01-Appendix 16.2.9.2] Report date: 26-May-2021 **Cardiac Safety Report** [Study PSMA-617-01-Appendix 16.2.9.3] Report date: 09-Jun-2021 **Radiation Dosimetry Report for [177Lu]Lu-PSMA-617** [Study PSMA-617-01-Appendix 16.2.9.4] Report date: 10-May-2021 **Imaging Study Report:** PSMA-617-01 Imaging Study Report: Reviewer Variability Reviewer Variability Report date: 17-Jun-2021
Protocol: PSMA-617-02 **Countries**: United States **Start**: 05-Jul-2018 **End**: 15-Jan-2020	**Design, purpose & population**: PSMA-directed endoradiotherapy of castration-resistant prostate cancer (RESIST-PC). A **Phase 2 Clinical Trial**	**Total**: 71 (randomized), 64 (treated) **Age**: 54-95 (70.3) years (randomized patients) **Groups**: 2 Group 1: 23 Group 2: 41	**Form(s)**: ^{177}Lu-PSMA-617 i.v. administration, infused over approximately 15-30 minutes using an infusion pump **Duration**: 24 months (treatment/assessment and follow-up) **Doses**: ^{177}Lu-PSMA-617, 6.0 GBq ^{177}Lu-PSMA-617, 7.4 GBq	**Study Status**: Complete **Report no**. [PSMA-617-02], full final **Report date**: 07-Jan-2021 **Other reports**: None

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

2.6.5.1. Dose response study(ies)

The applicant supported that the selection of the ^{177}Lu-PSMA-617 7.4 GBq dose for Study PSMA-617-01 was determined by considering prior clinical experience regarding efficacy and safety, dosimetric evaluation and radiosensitivity, and RLT class-based information from Lutathera.

Dosimetry and radiation safety considerations

At present, the absorbed radiation dose thresholds for different organ systems have not been completely defined for RLTs, with existing thresholds being historically based on EBRT. The radiation dose administered during EBRT is frequently limited by the risk of long-term toxicities to adjacent organs as a consequence of treatment with high dose rate radiation, and these limits for EBRT have been estimated and published in the literature (Emami et al 1991, Dawson et al 2010, Marks et al 2010, Emami 2013). However, the application of these EBRT thresholds to RLT is likely too conservative due to the intrinsic differences between external and systemic radiotherapy treatment modalities and thus serves mainly as a guide for RLT dose selection, as opposed to a restrictive limit.

At the time of Study PSMA-617-01 protocol development, 11 dosimetry studies in over 100 patients had been conducted and published. The results were consistent across the studies, and demonstrated exposure that correlated well with the expected rapid clearance of a small molecule, and the limited distribution pattern of a PSMA-targeted RLT. The primary sites of non-tumor uptake reported in these published dosimetry studies were the salivary glands, lacrimal glands, and kidneys, with excretory mechanisms and PSMA expression in the proximal tubules contributing to exposure in the kidneys (please refer to the PK part of this AR for details).

Approximately 50% of the injected dose was shown to be excreted in the urine within the first 48 hours. Additionally normal bone marrow, although PSMA-negative, can be exposed transiently to ^{177}Lu-PSMA-617 while in circulation, or through proximal exposure from the uptake in neighboring PSMA-positive PC bone lesions, a common site of metastasis. The bone marrow also represents a radiosensitive tissue due to its proliferative nature; therefore, the bone marrow radiation absorbed dose was also a consideration.

When determining the dose for Study PSMA-617-01, a more specific consideration of cumulative radiation exposure in these tissues was considered due to multi-cycle treatment with ^{177}Lu-PSMA-617.

Class-based evidence (Lutathera)

Lutathera was the first approved peptide-based ^{177}Lu-radioligand therapeutic in NET-Tumours, and utilizes a dose of 7.4 GBq every 8 weeks for a total of 4 cycles, although other doses and schedules have been evaluated in the literature. The published experience with Lutathera informed much of the early development work that has been done with ^{177}Lu-PSMA-617. Considering Lutathera as a comparator is particularly relevant, as the kidney dosimetry profile for both agents is similar, due to the renal clearance of both agents, as well as their target expression on the renal proximal tubules.

Based on the extensive clinical experience with Lutathera, the kidney absorbed radiation dose thresholds in RLT were suggested to be higher than the EBRT threshold for kidneys suggested by several authors (Wessels et al 2008, Bergsma et al 2016).

Previous Experience with ^{177}-Lu-PSMA

Recent publications show that cumulative doses of 30 to 60 GBq of ^{177}Lu-PSMA-617 may be possible without adverse effects on renal tissue (Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017), 45 to 73.8 GBq for hematological tissue (Kabasakal et al 2017, Scarpa et al 2017), and 50 GBq for salivary glands (Virgolini et al 2018).

The **majority of the publications used a regimen of 4 cycles of 6 GBq every 8 weeks**. However, efficacy and safety information from the prospective Phase II study by Hofman et al (2018) suggested that dosing of 4.4 to 8.7 GBq (mean: 7.5) every 6 weeks for 4 cycles was well tolerated and efficacious in patients with mCRPC.

However, there were also reports of more than 4 cycles of ^{177}Lu-PSMA-617 being administered safely as a means to maximize the benefit to the patient (Rahbar et al 2018); therefore, the 2 additional cycles (resulting in a maximum of 6 cycles) were incorporated into the Study PSMA-617-01 protocol under the condition that benefit and tolerability were confirmed following the 4th cycle.

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

Proposed posology

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

- Median rPFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 6.4 months (95% CI: 4.3, 7.9); for patients who received 5-6 cycles, median rPFS was 13.8 months (95% CI: 12.2, 17.0).
- Median OS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 11.0 months (95% CI: 9.6, 12.6); for patients who received 5-6 cycles, median OS was 24.7 months (95% CI: 21.3, 27.6).
- Median PFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.4 months (95% CI: 3.3, 4.7); for patients who received 5-6 cycles, median PFS was 9.9 months (95% CI: 8.6, 11.3).
- Median time to worsening in FACT-P total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.4 months (95% CI: 4.2, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-P total score was 9.2 months (95% CI: 8.3, 11.1). Median time to worsening in FACT-G total score for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.6, 6.0); for patients who received 5-6 cycles, median time to worsening in FACT-G total score was 10.3 months (95% CI: 8.8, 11.4).
- Median time to worsening in BPI-SF pain intensity for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 4.7 months (95% CI: 3.1, 5.7); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain intensity was 9.4 months (95% CI: 8.5, 10.8).
- Median time to worsening in BPI-SF pain interference for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.4, 6.0); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain interference was 8.8 months (95% CI: 7.4, 10.4).

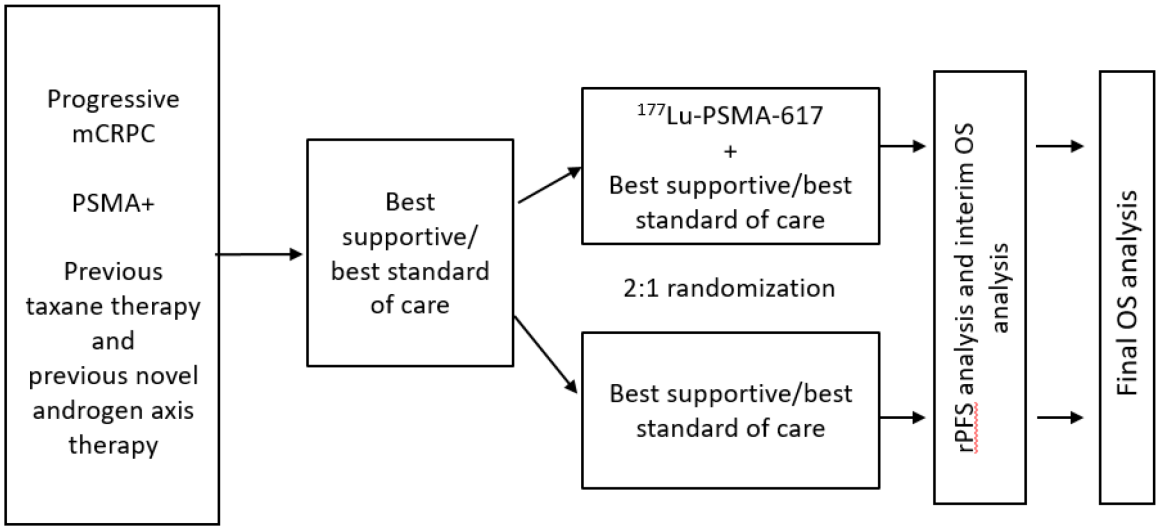
- AEs were also assessed in patients who received ≤4 cycles of ^{177}Lu-PSMA-617 and in those who received 5 or 6 cycles. Overall, there was no suggestion of a safety concern in patients who received more cycles.

2.6.5.2. Main study(ies)

Trial PSMA_617-01

"VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)"

Figure 6: Study design



Methods

Study Participants

Diagnosis and main criteria for inclusion: Adult male patients who had a histological, pathological, and/or cytological confirmation of PC, progressive mCRPC (based on any one of the following as defined by the prostate cancer clinical trials working group 3 (PCWG3) criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease), had received at least 1 novel androgen axis drug (NAAD), were previously treated with at least 1 but no more than 2 prior taxane regimens and had a positive ^{68}Ga-PSMA-11 PET/CT scan, as determined by the Sponsor's central reader.

Main criteria for exclusion: Patients with previous treatment with any of the following within 6 months of randomization: strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223, or hemi-body irradiation or previously treated with PSMA-targeted targeted radioligand therapy (RLT), or

any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy) within 28 days prior to day of randomization were excluded. These criteria and other safety related exclusion criteria would potentially increase the heterogeneity of the population and may cause bias. Thus, they are also acceptable.

Treatments

^{177}Lu-PSMA-617 was administered as a slow i.v. injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles. It was administered only by qualified/authorized personnel. Treatment with ^{177}Lu-PSMA-617 was performed in accordance with national and/or local radiation safety requirements. Due to nature of this drug product there was 1 batch number for each patient dose.

BSC/BSoC was prescribed by each patient's physician and reflected standard interventions available to clinicians. BSC/BSoC regimen could be adapted during the study to the best interest of the patient at the discretion of the Investigator, however investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223), or hemi-body radiotherapy treatment were not allowed during the study.

Objectives

Primary objective

The primary objective of the pivotal trial PSMA-617-01 was to compare the 2 alternate endpoints of radiographic- progression-free survival (rPFS) and OS in patients with progressive prostate-specific membrane antigen (PSMA)-positive mCRPC who received ^{177}Lu-PSMA-617 in addition to best supportive/best standard of care (BSC/BSoC) versus patients treated by BSC/BSoC only.

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

Key secondary objectives

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

- Response evaluation criteria in solid tumours (RECIST) response:
    - Overall response rate (ORR) as measured by RECIST v1.1 and
    - Disease control rate (DCR) as measured by RECIST v1.1
- Time to a first symptomatic skeletal event (SSE)

Key secondary endpoints were assessed using the Hochberg closed test procedure at the alpha level applicable to the successful OS endpoint. This procedure is reasonable given the positive correlation between the key secondary endpoints.

Additional secondary objectives

- Safety and tolerability of ^{177}Lu-PSMA-617
- Periodic assessment of health-related quality of life (HR QoL) to evaluate impact of intervention on patient well-being (EuroQol 5-Dimensions 5-Level (EQ-5D-5L) questionnaire, functional assessment of cancer therapy – prostate (FACT-P) questionnaire, and brief pain inventory – short form (BPI-SF))
- Health economics

Progression-free survival (PFS) (radiographic, clinical, or PSA) Biochemical response as measured by

prostate-specific antigen (PSA). Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels were also collected.

Outcomes/endpoints

Primary endpoints;

"Alternate primary endpoints"

- **rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on the central review assessment per the PCWG3 criteria or death due to any cause.** Patients who were alive without radiographic progression at the analysis data cut-off were censored for rPFS at the time of their last evaluable radiographic assessment.

The null hypothesis for rPFS, assumed the median rPFS was 4 months on active treatment for a HR of 1.00. Under the alternative hypothesis, median rPFS on active treatment was assumed to be 6 months for a HR of 0.67.

- **OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient was not known to have died, then OS was censored. The censoring date was date of the last study visit, or contact, until the cut-off date. The cut-off date was not used for last contact date, unless the patient was seen or contacted on that date.**

The null hypothesis for survival, assumed median OS was 10 months on active treatment for a HR of 1.00. Under the alternative hypothesis, median OS on active treatment was assumed to be 13.7 months for a HR of 0.7306.

Key secondary endpoints

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

- Response evaluation criteria in solid tumours (RECIST) response:
  - **Overall response rate (ORR)** as measured by RECIST v1.1
  - **Disease control rate (DCR)** as measured by RECIST v1.1
- **Time to a first symptomatic skeletal event (SSE)**.

Additional secondary endpoints

- Safety and tolerability of ^{177}Lu-PSMA-617
- Periodic assessment of health-related quality of life (HR QoL) to evaluate impact of intervention on patient well-being (EuroQol 5-Dimensions 5-Level (EQ-5D-5L) questionnaire, functional assessment of cancer therapy – prostate (FACT-P) questionnaire, and brief pain inventory – short form (BPI-SF))
- Health economics
- Progression-free survival (PFS) (radiographic, clinical, or PSA)
- Biochemical response as measured by prostate-specific antigen (PSA). Alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) levels were also collected.

Sample size

Based on a non-linear patient accrual profile over 14 months, a total of 814 patients randomized and followed on an ITT basis for a minimum of 13 months was expected to yield 508 deaths.

This number of events provided at least 90% power to test the hypothesis that the HR for OS is 1.00 with the alternative 0.7306 or better with a 1-sided alpha level of at least 0.020.

For rPFS, a total of approximately 557/814 patients were expected to be randomized on or after 05-Mar-2019, these being the patients of the primary analysis of rPFS; with a minimum of approximately 6 months follow-up, these patients were expected to yield 364 rPFS events which was sufficient to provide 84% power to test the hypothesis that the HR of rPFS is 1.00 with the alternative 0.67 or better with a 1-sided alpha level of 0.004.

Randomisation and Blinding (masking)

Patients were randomized by an IRT in a 2:1 ratio to the investigational treatment arm (^{177}Lu-PSMA-617+BSC/BSoC) or to the control arm (BSC/BSoC-only) using a permuted block scheme. Randomization was stratified by the following 4 factors:

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

As other trial investigating a RLT-product, blinding is not possible since normal radiation detectors used for safety reasons easily unblind the patient's treatment allocation. Thus, it is agreed that the study was performed open label.

Statistical methods

The planned analyses and statistical methods are described in the final version of the statistical analysis plan which was written and approved prior to database lock.

The following analysis sets were used for efficacy analysis in this study:

Full Analysis Set (FAS): All randomized patients. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This is an intent to treat (ITT) analysis set. This analysis set is used for the analysis of OS.

PFS Full Analysis Set (PFS-FAS): All patients randomized on or after 05-Mar-2019. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.

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

rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on the central review assessment per the PCWG3 criteria or death due to any cause. The censoring date was the date when the last evaluable radiographic assessment (CT/MRI/bone scan) determined a lack of progression. Patients who had 2 or more consecutive missed tumor assessments immediately prior to PD or death were censored at the date of the last evaluable tumor assessment prior to those missing tumor assessments.

OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient was not known to have died, then OS was censored. The censoring date was date of the last study visit, or contact, until the cut-off date.

The primary analysis for rPFS was to test the null hypothesis of a HR of 1.00 and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The primary analysis of rPFS was based on the PFS-FAS population. The rPFS distribution was estimated using the Kaplan-Meier method.

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

The primary analysis of OS was based on the FAS population. For analysis of OS, the same statistical methods were used than for rPFS.

ORR and DCR were analyzed using logistic regression with a single covariate for randomized treatment arm and stratification for the randomization stratification factors. DOR was analyzed in the Response Evaluable Analysis Set using mixture distribution methodology. Time to first SSE was summarized and analyzed in the same manner as described for rPFS using the PFS-FAS.

The null hypothesis for rPFS was tested with an alpha level of 0.004 (one-sided). The alpha level applicable to OS in the final analysis would depend upon the earlier rPFS and interim OS results (with alpha=0.001 spent for the interim OS analysis). The interim analysis was not completed as the targeted number of OS events were observed before the targeted number of rPFS events. Therefore, the alpha level applicable to OS in the final analysis depends upon the final rPFS results: if $p < 0.004$ one-sided is achieved for rPFS, then the alpha level for the final analysis of OS is raised to 0.025 1-sided; if $p < 0.004$ one-sided is not achieved for rPFS, then the alpha level for the final analysis of OS is 0.021 one-sided.

To control the overall Type I error rate, if either alternate primary endpoint was met, key secondary endpoints were assessed using the Hochberg closed test procedure.

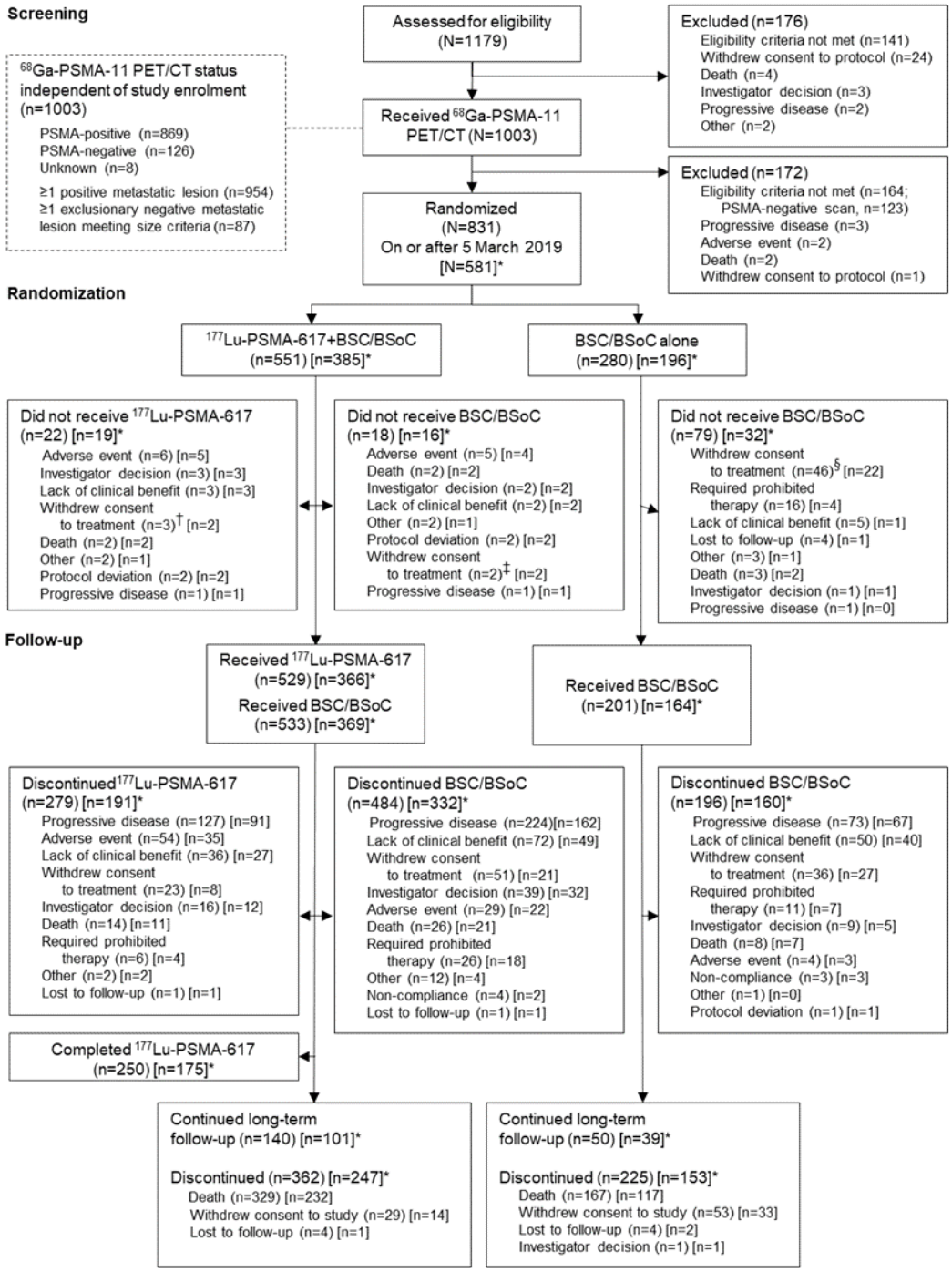
Sensitivity and supportive analyses were performed to assess the overall robustness of the rPFS results. A supplementary analysis of rPFS was also performed using the FAS population.

Supplementary and sensitivity analyses were performed to assess the overall robustness of the OS results. A supplementary descriptive analysis of OS was performed using the PFS-FAS population. In addition to the primary analysis of OS, a supplementary OS analysis was conducted based on the first 750 patients randomized in the FAS. A sensitivity analysis to assess the impact of COVID-19 included analysis per primary OS analysis but censoring COVID-19 related deaths at the date of death.

Results

Participant flow

Figure 7: Patient disposition in PSMA-617-01 (All screened patients)



* Number in square brackets indicate patients randomized on or after 05-Mar-2019, see [Study PSMA-617-01-Section 9.2].

† Reasons for withdrawal of consent to treatment: none given (n=2), travel or procedure "fatigue" (n=1)

‡ Reasons for withdrawal of consent to treatment: none given (n=1), travel or procedure "fatigue" (n=1)

§ Reasons for withdrawal of consent to treatment: receiving BSC/BSoC without ^{177}Lu-PSMA-617 (n=31), none given (n=7), decided to pursue off-study treatment (n=5), travel or procedure "fatigue" (n=2), perceived lack of benefit (n=1)

"Completed ^{177}Lu-PSMA-617" indicates completed at least 4 cycles as reported by the investigator;

Source [Study PSMA 617-01-Figure 10.1].

Recruitment

Study initiation date: 29-May-2018 (first patient first visit)

Data cut-off date: 27-Jan-2021 - The required number of overall survival (OS) events was reached to trigger the final OS analysis and primary analysis of rPFS of this study. Enrollment has ended but the study is still ongoing

Conduct of the study

In total 5 amendments in the study protocol and 4 in the Imaging Endpoint Imaging Manual were performed in the trial. As detailed above, particular in the second amendment of the study protocol major amendment regarding the objectives and endpoints were performed. It was clarified that the changes introduced are not likely to have affected the integrity of the study.

Protocol deviations were generally more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm, which seems to be related mainly by the longer duration of exposure in this arm (PSMA: 50.6% vs BSC: 38.6%)

Baseline data

Overall, a total of 831 patients were randomized and included in the FAS population; 75.3% of whom were ≥ 65 years and 92.4% had an ECOG PS score of 0-1. The median time since initial diagnosis was 7.4 years (range: 0.7, 28.9), almost all (96.3%) had at least one PC-related surgery (including biopsies), and 43.2% had received therapeutic surgery. The majority of patients (76.1%) also had at least one PC-related radiotherapy, and 79.1% had received more than 3 different regimens of prior systemic therapy. All patients had received prior taxane treatment and a prior AR pathway inhibitor [There was a low representation of patients who were Black or African American (6.6% of patients overall) or Asian (2.4%).

The demographic and baseline disease characteristics (including prognostic factors) were well balanced between the two treatment arms. The population of patients reflects the target population, for whom the drug is intended, namely heavily pre-treated patients with progressive PSMA-positive mCRPC. No obvious bias due to disease characteristics was revealed from this data after study amendment and change of the endpoint. A comparison demonstrated that stratification factors were well balanced between the 2 randomized arms at baseline and in the FAS. Subgroup characteristics regarding age are shown below:

Table 9: Subgroup characteristics - age groups (<65, 65-74, 75-84, >=85) (Study PSMA-617-01, Full analysis set)

	^{177}Lu-PSMA-617 +BSC/BSoC (N=551) n (%)	**BSC/BSoC only (N=280) n (%)**	**Overall (N=831) n (%)**
Age (categorized)			
<65 years	145 (26.3)	60 (21.4)	205 (24.7)
65-74 years	254 (46.1)	128 (45.7)	382 (46.0)
75-84 years	144 (26.1)	86 (30.7)	230 (27.7)
>=85 years	8 (1.5)	6 (2.1)	14 (1.7)
Data Cutoff Date: 27JAN2021 [CHMP D120 Appendix Q66-Table 8.11.2a]			

Numbers analysed

Analysis sets

Full Analysis Set (FAS): All randomized patients. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This is an **intent to treat (ITT)** analysis set. This analysis set is used for the analysis of OS.

PFS Full Analysis Set (PFS-FAS): All patients randomized on or after 05-Mar-2019. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. This analysis set is used for the primary analyses of rPFS and all secondary endpoints except ORR and DCR.

Response Evaluable Analysis Set: The subset of patients in the PFS-FAS with evaluable disease by RECIST at baseline (i.e. at least one target and/or non-target lesion per independent central review radiologist assessment used as the final radiology assessment). Patients were included in the treatment arm to which they were randomized. Soft tissue response as measured by RECIST was assessed in this dataset. This analysis set was used for the primary analyses of ORR and DCR.

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

PSMA-11 Safety Analysis Set: All patients who received a dose of ^{68}Ga-PSMA-11. This included screened patients who were not randomized. Randomized patients were included in the treatment arm to which they were randomized.

Table 10: Analysis sets in trial PSMA-617-01(All screened patients)

	Not enrolled [1] N=348 n (%)	**Lu-PSMA-617 +BSC/BSoC N=551 n (%)**	**BSC/BSoC only N=280 n (%)**	**Overall N=1179 n (%)**
PSMA-11 safety analysis set	172 (49.4)	551 (100)	280 (100)	1003 (85.1)
Full analysis set (FAS)		551 (100)	280 (100)	831 (70.5)
PFS full analysis set (PFS-FAS)		385 (69.9)	196 (70.0)	581 (49.3)
Response evaluable analysis set		319 (57.9)	120 (42.9)	439 (37.2)
FAS safety analysis set [2]		529 (96.0)	205 (73.2)	734 (62.3)

[1]: Patients who were not randomized to the study.
[2]: For the safety analysis set, the patients were included in the treatment arm corresponding to the actual treatment received (e.g. BSC/BSoC only if they were randomized to ^{177}Lu-PSMA-617+BSC/BSoC but received only BSC/BSoC).
Source: [Study PSMA-617-01-Table 14.1.3]

The higher proportion of patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm included in the Response evaluable analysis set (57.9% vs. 42.9%) and in the FAS safety analysis set (96.0% vs. 73.2%) may be related to the higher rate of early drop-out in patients randomized to BSC/BSoC only.

Outcomes and estimation

The **primary objective** of this study is to compare the **two alternate endpoints, rPFS and OS**, in patients with progressive PSMA-positive mCRPC who received **^{177}Lu-PSMA-617+BSC/BSoC versus** patients treated by **BSC/BSoC only**.

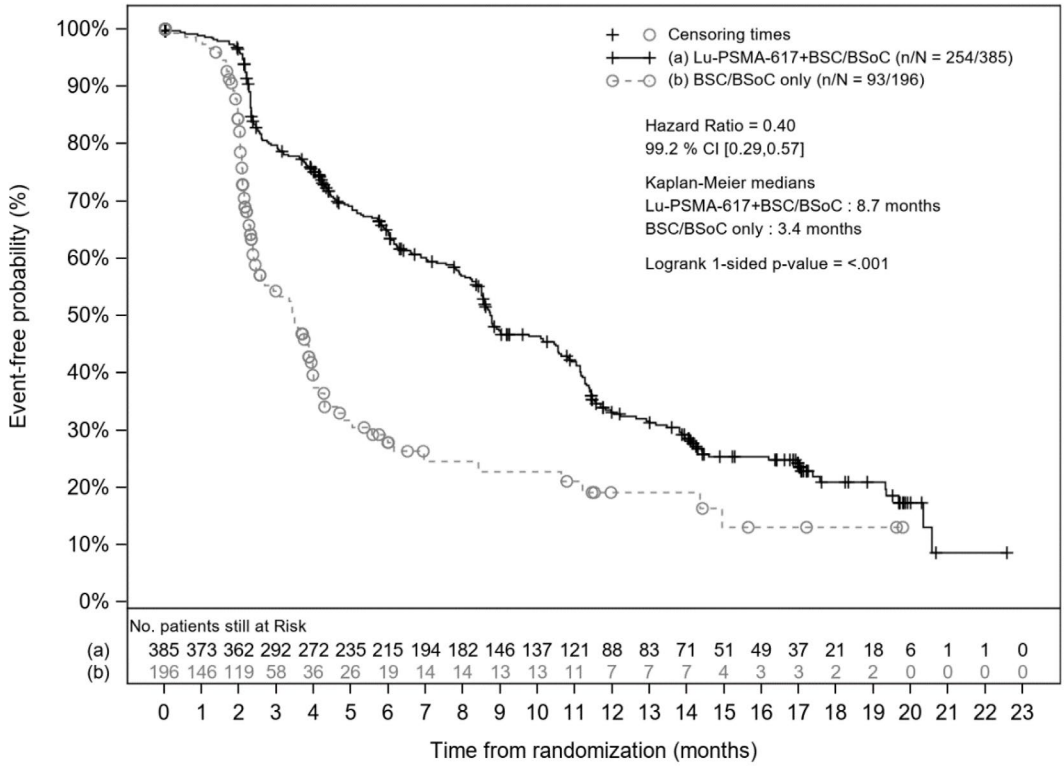
The primary analysis of rPFS was planned to be conducted when 364 rPFS events had been observed in patients randomized on or after 05-Mar-2019 with an interim analysis of OS at the time of the rPFS analysis using all patients randomized since study commencement. A final analysis of OS, using all patients randomized, was planned to take place when 508 deaths have been observed.

Alternate primary endpoint

1. **Radiographic progression-free survival (rPFS) per BICR: primary analysis based on PFS-FAS**

The study met its primary objective, demonstrating a **statistically significant improvement in rPFS based on BICR per PCWG3 criteria for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC** compared to patients receiving BSC/BSoC only (PFS-FAS; stratified log-rank test **p < 0.001, one-sided**). There was an **estimated 60% risk reduction of radiographic disease progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm** compared with the BSC/BSoC only arm (HR=0.40; 99.2% CI: 0.29, 0.57; Figure 9).

Figure 8: Kaplan-Meier plot of rPFS per blinded independent central review (PFS-FAS)



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

There were 254 events (66.0%; 171 radiographic progression events and 83 deaths) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 93 events (47.4%; 59 radiographic progression events and 34 deaths) in the BSC/BSoC only arm. The median rPFS was prolonged by 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (Table 15).

Table 11: Analysis of rPFS per blinded independent central review using stratified log-rank test and Cox regression model (PFS-FAS)

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

[1] Patients censored without adequate post-baseline evaluations or adequate baseline assessment.
[2] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[3] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs no). IRT data for stratification are used.
[4] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for death or radiographic progression.
Source: [Study PSMA-617-01-Table 14.2.2.1]

The **median follow-up time for rPFS in the PFS-FAS differed between the treatment arms (16.4 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 3.9 months in the BSC/BSoC arm)**. The estimated rPFS rates at 6 months were 64.6% vs. 27.8%, in the ^{177}Lu-PSMA-617+BSC/BSoC and BSC/BSoC only arms, respectively.

The Kaplan-Meier curves for rPFS per BICR diverged after approximately 8 weeks, corresponding to the time of first post-baseline tumor assessment, with the **radiographic progression-free probability remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm than for the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy** (Figure 9).

The censoring rate for rPFS differed between the treatment arms (34.0% vs. 52.6%); there was a greater proportion of patients who were ongoing without an event in the ^{177}Lu-PSMA 617+BSC/BSoC arm compared to the BSC/BSoC only arm (23.4% vs. 12.2%). Censoring reasons other than 'ongoing without an event' were lower in the ^{177}Lu-PSMA-617+BSC/BSoC arm relative to the BSC/BSoC only arm.

In addition, rPFS was analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set also by number of ^{177}Lu-PSMA-617 cycles. Median rPFS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 6.4 months (95% CI: 4.3, 7.9), and median rPFS for patients who received 5-6 cycles of ^{177}Lu-PSMA-617 was 13.8 months (95% CI: 12.2, 17.0) [SCE Appendix 1-Table 14.2.2.20].

Sensitivity analyses of rPFS per BICR

No formal statistical test of hypotheses was performed for these sensitivity analyses. Sensitivity analyses were conducted as follows for the primary endpoint rPFS:

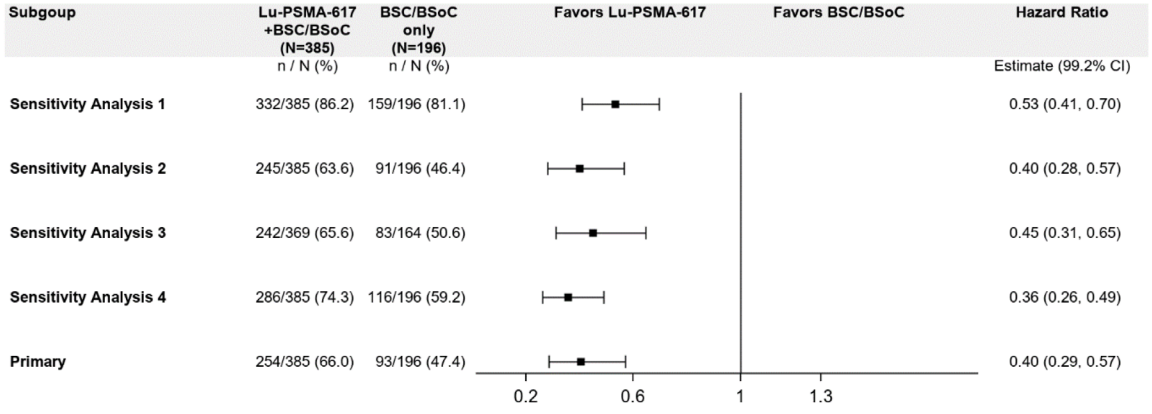
- Sensitivity analysis 1:

Includes events regardless of intervening missed assessments. Bone PDs were indicated per PCWG3 guidelines with modified rules for confirmation after Week 16. Included all radiographic PD and deaths captured in the study, including scans not centrally read that were captured on the lost to follow-up CRF page

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

A forest plot of HR with 99.2% CI for the 4 rPFS sensitivity analyses and primary analysis is presented in Figure 10. All 4 sensitivity analyses support the rPFS primary endpoint analysis based on the PFS-FAS and favor the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Figure 9: ***Sensitivity analyses of rPFS per blinded independent central review– forest plot of HR with 99.2% CI (PFS-FAS)***

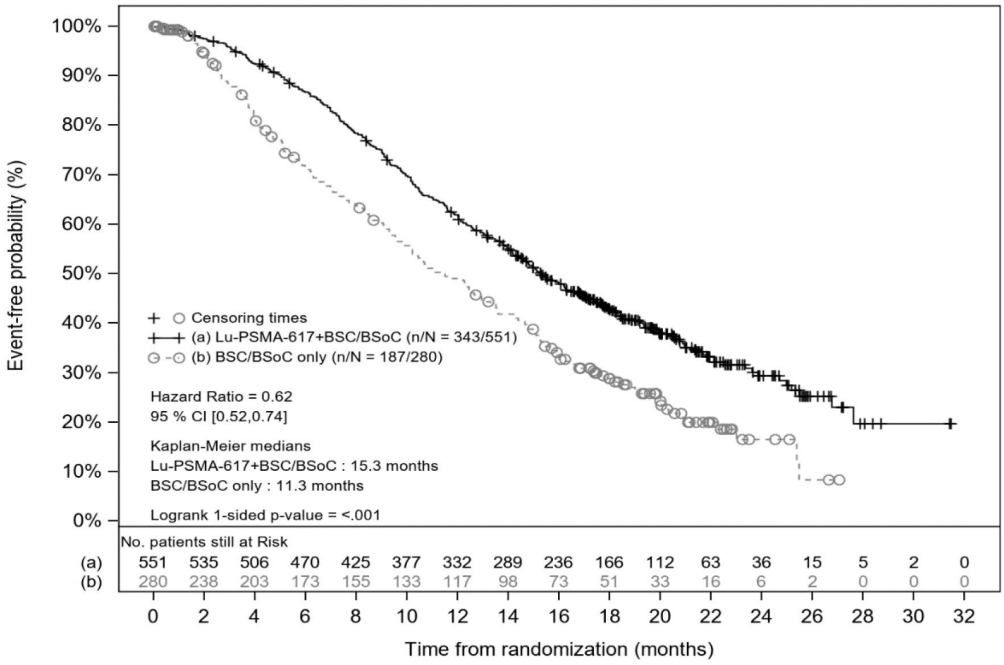


n/N: number of events/number of patients in treatment arm.
Vertical line shows no effect point.
Source: [Study PSMA-617-01-Figure 14.2.2.3]

2. Overall survival: primary analysis based on the FAS

The study met its primary objective, demonstrating a statistically significant improvement in OS for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 38% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.62; 95% CI: 0.52, 0.74; Figure 11, Table 16).

Figure 10: Kaplan-Meier plot of OS (FAS)



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

There were 343 deaths (62.3%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 187 deaths (66.8%) in the BSC/BSoC only arm. The median OS was prolonged by 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The median follow-up times for OS in the FAS were similar between the treatment arms (20.3 months [95% CI: 19.8, 21.0] vs. 19.8 months [95% CI: 18.3, 20.8] in the ^{177}Lu-PSMA- 617+BSC/BSoC and the BSC/BSoC only arms, respectively). The estimated OS rates at 12 months were 61.7% vs. 49.0%, in the ^{177}Lu-PSMA-617+BSC/BSoC and the BSC/BSoC only arms, respectively.

The Kaplan-Meier curves for OS diverged after approximately 2 months, remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy (Figure 11).

The censoring rate for OS differed between the treatment arms (37.7% vs. 33.2%); this appeared to be mainly due to 1) a greater percentage of patients who were alive in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, and 2) fewer patients who withdrew consent in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (Table 16).

Table 12: Analysis of OS using stratified log-rank test and Cox regression model (FAS)

	^{177}Lu-PSMA-617+BSC/BSoC N=551	**BSC/BSoC only N=280**
OS, n (%)		
Deaths	343 (62.3)	187 (66.8)
Censored	208 (37.7)	93 (33.2)

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

[1] Patients without event and still on study at data cut-off date.
[2] Patients who discontinued the study for reasons other than withdrew consent.
[3] Patients who withdrew consent from the study.
[4] Hazard Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only.
[5] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used.
[6] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for deaths.
Source: [Study PSMA-617-01-Table 14.2.1.1]

Analysis of OS based on first 750 patients randomized (Primary endpoint Assessment before Amendment 2)

In addition to the primary analysis of OS, a supplementary OS analysis was conducted based on the first 750 patients randomized in the FAS. The results were similar to those for the primary analysis of OS, with a statistically significant improvement in OS for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 37% risk reduction of death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.63; 95% CI: 0.52, 0.77) [SCE Appendix 1-Figure 14.2.1.1.3].

In addition, OS was analysed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. Median OS for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 11.0 months (95% CI: 9.6, 12.6), and median OS for patients who received 5-6 cycles of ^{177}Lu-PSMA-617 was 24.7 months (95% CI: 21.3, 27.6) [SCE Appendix 1-Table 14.2.1.12].

Analyses to assess sensitivity of rPFS and OS to censoring due to dropouts

A panel of analyses were performed to assess sensitivity of rPFS and OS to censoring due to drop-outs. The censoring events of principal interest for analysis were "adequate assessment not available" for rPFS, and "lost to follow-up" and "withdrawal of consent" for OS. The four types of analyses that were performed used published and accepted methods (Lu et al 2015; Atkinson et al 2019).

The extreme case analysis considered all drop-outs in the ^{177}Lu-PSMA-617+BSC/BSoC arm as events. The two best case analyses imputed data for drop-outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSC/BSoC only arm.

The event risk inflation/deflation analysis was based on plausible ranges of increased and decreased risk considering possible treatment options after drop-out, with a treatment-specific inflation factor. The tipping-point analysis quantified the increase or decrease in the risk of event in patients dropping out of the ^{177}Lu-PSMA-617+BSC/BSoC arm or BSC/BSoC only arm that would make the primary analysis lose statistical significance.

The results of these sensitivity analyses were consistent with the primary analyses of rPFS and OS (Table 17).

Table 13: Sensitivity analyses of rPFS and OS assessing impact of censoring due to drop-outs

rPFS (PFS-FAS)	**Scenario**	**HR (99.2% CI)**
Analysis per protocol	Censored as it is	0.4 (0.29, 0.57)
Extreme case	The selected extreme case scenario	0.42 (0.3, 0.6)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.77 (0.55, 1.07)
Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.56 (0.4, 0.79)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.4 (0.29, 0.56)
Multiple imputation under informative censoring	Hazard decrease by 60% in BSC/BSoC arm after censoring*	0.54 (0.38, 0.77)
Tipping point 1: 99.2% CI above 1	Hazard decrease by 85% in BSC/BSoC arm after censoring*	0.71 (0.5, 1.01)
Tipping point 2: Extreme case	Hazard decrease by 11% in BSC/BSoC arm after censoring*	0.42 (0.3, 0.59)
OS (FAS)	**Scenario**	**HR (95% CI)**
Analysis per protocol	Censored as it is	0.62 (0.52, 0.74)
Extreme case	The selected extreme case scenario	0.66 (0.55, 0.79)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.8 (0.67, 0.96)

Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.76 (0.64, 0.91)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.63 (0.53, 0.76)
Multiple imputation under informative censoring	Hazard decrease by 38% in BSC/BSoC arm after censoring*	0.68 (0.56, 0.82)
Tipping point 1: largest upper 95% CI	Hazard decrease by 99% in BSC/BSoC arm after censoring*	0.84 (0.7, 1.00)
Tipping point 2: Extreme case	Hazard decrease by 27% in BSC/BSoC arm after censoring*	0.66 (0.55, 0.79)

*Risk of event remains unchanged after censoring in the investigational arm (^{177}Lu-PSMA-617+BSC/BSoC arm).
Source: [SCE-Appendix 1-Table 29, Table 30]

Key secondary efficacy results

All 3 key secondary efficacy objectives were met:

- **ORR** was statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test $p < 0.001$, two-sided), with ORR of 29.8% in the ^{177}Lu- PSMA-617+BSC/BSoC arm vs. 1.7% in the BSC/BSoC only arm (odds ratio 24.99; 95% CI: 6.05, 103.24); median DoR in responders was 9.8 months (95% CI: 9.1, 11.7) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (median DoR in the BSC/BSoC only arm was not reliable since only 1 of the 2 patients who responded had RECIST radiographic progression or death). In the subset of patients with measurable disease (at least 1 target lesion per BICR), ORR was 51.1% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 3.1% in the BSC/BSoC only arm, with an odds ratio of 37.61 (95% CI: 8.84, 159.99) [SCE Appendix 1-Table 14.2.3.1.1].
- **DCR** was also statistically significant in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm (stratified Wald's Chi-square test $p < 0.001$, two-sided), with DCR of 89.0% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 66.7% in the BSC/BSoC only arm (odds ratio 5.79; 95% CI: 3.18, 10.55). In the subset of patients with measurable disease (at least 1 target lesion per BICR), DCR also favored the ^{177}Lu-PSMA-617+BSC/BSoC arm, with a DCR of 86.4% in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 50.0% in the BSC/BSoC only arm (odds ratio=10.03; 95% CI: 4.50, 22.34) [SCE Appendix 1-Table 14.2.3.1.1].
- **Time to first SSE** favored the ^{177}Lu-PSMA-617+BSC/BSoC arm with an estimated 50% risk reduction of symptomatic skeletal event or death that was statistically significant (HR= 0.50; 95% CI: 0.40, 0.62; stratified log-rank two-sided p-value: < 0.001). There were 256 events (66.5%; 60 SSE events and 196 deaths) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 137 events (69.9%; 34 SSE events and 103 deaths) in the BSC/BSoC only arm. The median time to first SSE was delayed by 4.7 months, from 6.8 (95% CI: 5.2, 8.5) months in the BSC/BSoC only arm to 11.5 months (95% CI: 10.3, 13.2) in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The following Table 18 details the results regarding the key secondary outcomes:

Table 14: Analyses of ORR, DCR, and DoR per blinded independent central review (Response evaluable analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=319	**BSC/BSoC only N=120**
Best overall response (BOR), n (%)		
Complete Response (CR)	18 (5.6)	0
Partial Response (PR)	77 (24.1)	2 (1.7)
Stable Disease	68 (21.3)	30 (25.0)

	^{177}Lu-PSMA-617+BSC/BSoC N=319	**BSC/BSoC only N=120**
Non-CR/Non-PD	121 (37.9)	48 (40.0)
Progressive Disease (PD)	33 (10.3)	35 (29.2)
Unknown	2 (0.6)	5 (4.2)
Overall Response Rate (ORR: CR+PR), n (%)	95 (29.8)	2 (1.7)
Odds Ratio [95% CI] [1]	24.99 [6.05, 103.24]	
Two-sided p-value [1]	< 0.001	
Disease Control Rate (DCR CR+PR+Stable Disease+Non-CR/ Non-PD > 6 weeks), n (%)	284 (89.0)	80 (66.7)
Odds Ratio [95% CI] [1]	5.79 [3.18, 10.55]	
Two-sided p-value [1]	< 0.001	
Duration of Response (DoR) (months), n (%)		
N	95	2
Events (Progression or Death)	46 (48.4)	1 (50.0)
Radiographic progressions	29 (30.5)	1 (50.0)
Deaths	17 (17.9)	0
Censored	49 (51.6)	1 (50.0)
Ongoing without event	38 (40.0)	1 (50.0)
Event documented after 2 or more missed tumor assessments	11 (11.6)	0
Adequate assessment not available [2]	0	0
Kaplan-Meier estimates (months)		
25th percentile [95% CI]	6.9 [5.9, 8.3]	10.6 [NE, NE]
Median DoR [95% CI]	9.8 [9.1, 11.7]	10.6 [NE, NE]
75th percentile [95% CI]	18.0 [15.5, 18.0]	10.6 [NE, NE]
Mean DoR (months) [3]	12.5	10.6
SE DoR (months) [3]	0.009	0.000
EDoR (months) [3]	3.7	0.2
Ratio of EDoR and 95% CI [3]	21.05 [5.27, 84.05]	
Two-sided p-value [3]	< 0.001	

n: Total number of patients with a CR or PR.
[1] Odds Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only based on logistic regression model stratifying for the randomization stratification factors, LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in best supportive/standard of care at time of randomization (yes vs no). IRT data for stratification are used. P-value based on Wald's Chi-Square test.
[2] Patient censored without adequate post-baseline evaluations or adequate baseline assessment per RECIST v1.1.
[3] Analyzed using mixture distribution methodology (Ellis et al. 2008). DoR: duration of response in responding patients (months); SE: standard error; EDoR: expected duration of response (months) equals Mean DoR X Overall Response Rate.
Source: [Study PSMA-617-01-Table 14.2.3.1]

Additional secondary efficacy results

Progression-free survival

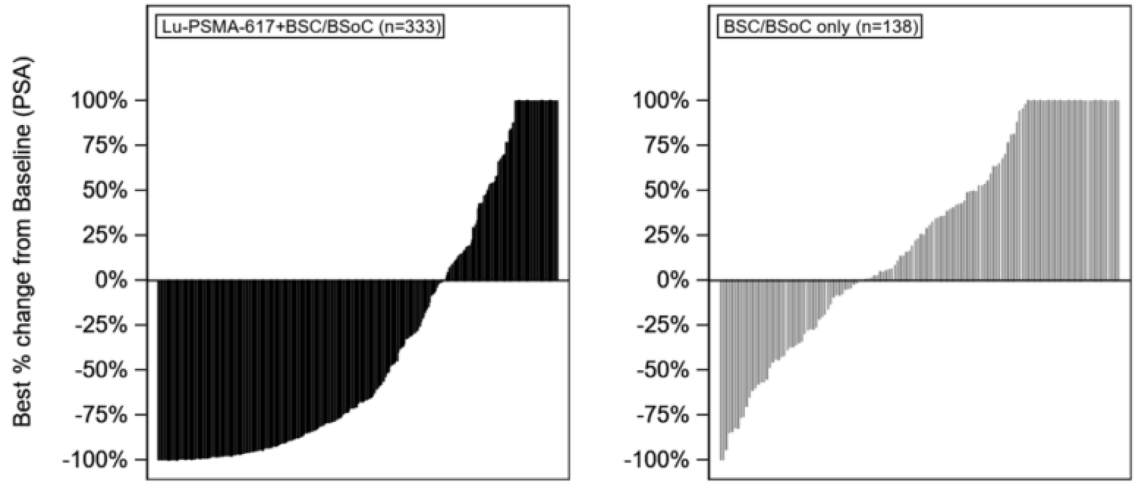
There was an estimated 70% risk reduction of radiographic disease progression based on BICR, clinical progression, PSA progression, or death (HR=0.30; 95% CI: 0.24, 0.38) in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Median PFS was 5.9 months (95% CI: 5.2, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.4 months (95% CI: 2.2, 3.0) in the BSC/BSoC only arm. Median PFS was 4.4 months (95% CI: 3.3, 4.7) for patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm who received 4 cycles, and 9.9 months (95% CI: 8.6, 11.3) for patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm who received 5-6 cycles.

Biochemical response

Prostate-specific antigen levels: Best percentage change from baseline in PSA level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 20.9% and 68.6% respectively in this arm, vs. mean and median increases of 50.4% and 24.3% in the BSC/BSoC only arm.

Figure 11: Waterfall plot of best percentage change from baseline in PSA level (PFS-FAS)



	Lu-PSMA-617+BSC/BSoC	BSC/BSoC
Decrease in best percentage change from baseline:	71.5%	35.5%
Increase/zero change in best percentage change from baseline:	28.5%	64.5%

Note: Increases greater than 100% have been truncated to 100% to display correctly the figure.
Patients for whom the best percentage change in PSA was not available were excluded from the analysis.
Source: [Study PSMA-617-01-Figure 14.2.5]

PSA doubling time, proportions of patients with PSA responses (≥ 50% and ≥ 80% decrease from baseline), and duration of PSA response were in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm. PSA response as ≥ 50% decrease from baseline occurred in 177/385 (46.0%; 95% CI: 40.9, 51.1) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 14/196 (7.1%; 95% CI: 4.0, 11.7) patients in the BSC/BSoC only arm. It should be noted that the proportion of patients evaluated for PSA doubling time was not balanced between the arms: 284/385 (73.8%) patients randomized to the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 74/196 (37.8%) patients randomized to the BSC/BSoC only arm.

Alkaline phosphatase levels

Mean and median baseline ALP levels were similar in both arms, while best percentage change from baseline in ALP level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 14.4% and 17.0% respectively in this arm vs. mean 0.6% increase and median 5.0% decrease respectively in the BSC/BSoC only arm.

Lactate dehydrogenase levels

Mean and median baseline LDH levels were similar in both arms, while best percentage change from baseline in LDH level favors the ^{177}Lu-PSMA-617+BSC/BSoC arm, with mean and median decreases of 23.1% and 23.3% respectively in this arm vs. mean and median decreases of 9.2% of 12.6% respectively in the BSC/BSoC only arm.

Patient-reported outcomes

PRO results confirmed previous findings in prostate cancer where disease-specific measures, such as FACT-P tend to be more sensitive in capturing HRQoL, as well as showing a treatment difference. For PRO analyses, worsening also includes clinical progression or death. FACT-P consistently showed an estimated 46% risk reduction in worsening from baseline in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to BSC/BSoC only arm across its many subscales and components. Specifically, median time

to worsening of the FACT-P total score was delayed by 3.5 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with a median time of 5.7 months (95% CI: 4.8, 6.6), compared to 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm.

Of note, by Cycle 3, approximately 84% of the patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 30% in the BSC/BSoC only arm had PRO data. By Cycle 5, the proportion of patients with data in the BSC/BSoC only arm had dropped to approximately 11%. PRO analyses should be interpreted with caution due to the relatively lower proportion of patients with PRO data in the BSC/BSoC only arm and the differential with the ^{177}Lu-PSMA- 617+BSC/BSoC arm, especially after Cycle 3. This is related to the relatively shorter period of time on study treatment in the BSC/BSoC only arm.

Summary of main efficacy results

The following Table 19 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).

Table 15: Summary of efficacy for the pivotal phase III trial trial PSMA-617-01

<table>
<tr><td colspan="3"><u>Title</u>: Trial PSMA_617-01
VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)</td></tr>
<tr><td>Study identifier</td><td colspan="2">PSMA-617-01, EudraCT no. 2018-000459-41, NCT03511664</td></tr>
<tr><td>Design</td><td colspan="2">Phase III, open-label, event-driven, international multi-center, randomized study to evaluate the efficacy and safety of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to BSC/BSoC as compared to BSC/BSoC only. Randomized patients were stratified on the following factors: LDH level (≤ or > 260 UI/L), presence of liver metastases (Yes or No), ECOG score (0-1 or 2) and inclusion of NAAD in the BSC/BSoC (at time of randomization, Yes or No).

Posology: ^{177}Lu-PSMA-617 was administered as a slow i.v. injection at a dose of 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles.

Duaration of treatment:
For the Test arm (¹⁷⁷Lu-PSMA-617+BSC/BSoC), at least 4 cycles and up to a maximum of 6 cycles of ¹⁷⁷Lu-PSMA-617, the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation.

For the Reference arm (BSC/BSoC only), there was no predefined number of cycles and the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation.</td></tr>
<tr><td></td><td>Study initiation date:
Data cut-off date::

Duration of Extension phase:</td><td>29-May-2018 (first patient first visit)
27-Jan-2021

all patients who consented to be in the long-term follow-up were to be followed for OS status every 3 ±1 months regardless of randomized treatment discontinuation reason</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority over BSC/BSoC alone</td></tr>
</table>

Title: Trial PSMA_617-01 *VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)*			
Treatments groups	**^{177}Lu-PSMA-617+BSC/BSoC (Test arm)**		**^{177}Lu-PSMA-617+BSC/BSoC** (at least 4 cycles and up to a maximum of 6 cycles of ^{177}Lu-PSMA-617, the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation.)
	BSC/BSoC only (Reference/Comparator Arm)		For the **Reference arm (BSC/BSoC only),** there was no predefined number of cycles and the patients could continue BSC/BSoC until they met one of the criteria for treatment discontinuation.
Endpoints and definitions	**Two alternate endpoints as primary objective**		
	Radiographic progression-free survival and **Overall survival**	**rPFS and OS**	**Radiographic progression-free survival (rPFS) and Overall survival (OS).** The statistical design of the study is such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it is not required to statistically meet both rPFS and OS to be declared a positive study.
	Key secondary Endpoints		
	Objective response rate	**ORR**	**1a) Objective response rate (ORR)** (CR + PR) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions. Duration of Response (DOR) will also be measured in patients with a CR or PR from date of first response to the date of RECIST progression or death.
	Disease Control Rate	**DCR**	**1b.)Disease Control Rate (DCR)** (CR + PR + stable disease [SD]) as measured by RECIST v1.1 response in soft tissue, lymph node and visceral lesions.
	The time to a first SSE		**2. The time to a first SSE** defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first.
	Additionally Secondary endpoints		
	1. Safety and Tolerability of ^{177}Lu-PSMA-617	**Drug-related Toxicity**	**Please refer to the safety part of this AR**
	2. Aspects of HRQoL	**PRO-QoL**	**Aspects of HRQoL** will be reported using the EuroQol 5-dimensions 5-level **[EQ-5D-5L] questionnaire**, Functional Assessment of Cancer Therapy – Prostate **[FACT-P]** questionnaire and Brief Pain Inventory – Short Form **[BPI-SF]**

Title: Trial PSMA_617-01 *VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)*			
	3. Health economics	**HE**	
	4.Progression-free survival	**PFS**	**4. Progression-free survival** a. **Radiographic progression** is defined as the date of radiographic disease progression as outlined in the Prostate Cancer Working Group 3 **(PCWG3)** Guidelines. b. **Unequivocal clinical progression**. Unequivocal evidence of clinical progression is defined as: **▪ Marked escalation in cancer related pain** that is assessed by the investigator to indicate the need for other systemic chemotherapy **▪ Immediate need for initiation of new anticancer treatment**, surgical or radiological intervention for complications due to tumor progression even in the absence of radiological progression **▪ Marked deterioration in ECOG performance status to ≥ Grade 3** and/or in the opinion of the investigator ECOG deterioration indicates clinical progression **▪ In the opinion of the investigator, it is in the best interest of the patient to discontinue treatment due to clinical progression** c. **PSA progression** is defined as the date that a ≥ 25% increase in PSA and an absolute increase of 2 ng/mL or more from the nadir is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (PCWG3 Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more after 12 weeks of treatment.
	5. Biochemical response endpoints (PSA; ALP, LDH)	**Biochem R**	**Biochemical response endpoints:** a. Proportion of subjects who are PSA responders, defined as a patient who has achieved a ≥50% decrease from baseline that is confirmed by a second PSA measurement ≥4 weeks. b. Alkaline phosphatase [ALP] and lactate dehydrogenase [LDH] levels will also be collected.
Database lock	27-Jan-2021 – (The required number of overall survival (OS) events was reached to trigger the final OS analysis and primary analysis of rPFS of this study. Enrollment has ended but the study is still ongoing.)		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: Trial PSMA_617-01

VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

Analysis population and time point description	**Intent to treat** **Planned to be randomized:** N=814 **Assessed for eligibility:** N=1179; (Received ^{68}Ga-PSMA-11 positron emission tomography/ computed tomography (PET/CT): N=1003) **Total Randomized:** N=831 (on or after 05-Mar-2019: N=581); **Randomized to 177Lu-PSMA-617+BSC/BSoC: N=551 (on or after 05-Mar-2019: N=385);** **Randomized to BSC/BSoC only:** N=280 (on or after 05-Mar-2019: N=196).			
Descriptive statistics and estimate variability	Treatment group	**177Lu-PSMA-617+BSC/BSoC**	**BSC/BSoC only**	**Conclusion**
	Number of subject	551	280	
	Primary Endpoints			
	Two alternate endpoints: as primary objective **rPFS and OS**			Statistically significant in favor of the 177Lu-PSMA-617+BSC/ BSoC arm (stratified Log-rank test p < 0.001, one-sided), for both endpoint components.
	rPFS (in PFS-FAS)	8.7 months (7.9, 10.8)	3.4 months (2.4, 4.0)	The median rPFS was prolonged by 5.3 months in the 177PSMA617+BSC/BSoC arm.
	OS -Median OS (in FAS)	15.3 months (14.2, 16.9)	11.3 months (9.8, 13.5)	The median OS was prolonged by 4.0 months in the 177PSMA617+BSC/BSoC arm.
	Key secondary Endpoints			
	ORR (PFS-FAS)	**29.8%**	**1.7%**	ORR was statistically significant in favor of the 177Lu-PSMA-617+ BSC/BSoC arm **(p < 0.001).**
	DoR (Median)	9.8 months (95% CI 9.1,11.7)	NR	Not reliable since only 1 of the 2 patients who responded had a RECIST radiographic progression or death

Title: Trial PSMA_617-01

VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

	DCR (PFS-FAS)	89.0%	66.7%	The DCR was also statistically significant in favor of the 177Lu-PSMA-617+BSC /BSoC arm (**p < 0.001).**
	Time to first SSE (Median) (in PFS-FAS)	11.5 months (10.3, 13.2)	6.8 months (5.2, 8.5)	Time to first SSE was also statisti-cally significant in favor of the 177Lu -PSMA-617+BSC/ BSoC arm **(p < 0.001)**, with an estimated 50% risk reduction of SSE or death in the 177Lu-PSMA-617+BSC/BSoC arm vs. the BSC/BSoC only arm (HR=0.50; 95% CI: 0.40, 0.62).
	Additionally Secondary endpoints			
	Drug-related Toxicity			
	PFS (Median) (in PFS-FAS)	5.9 months (95%CI:5.2,6.6)	2.4 months (95% CI: 2.2,3.0)	An estimated 70% risk reduction of radiographic disease progression based on BICR, clinical progression, PSA progression, or death (HR=0.30; 95% CI: 0.24, 0.38) in favor of the 177Lu-PSMA-617+BSC/BSoC arm (p < 0.001)
	PRO-QoL			
	FACT-P total score (Median) (in PFS-FAS)	5.7 months (95% CI: 4.8,6.6)	2.2 months (95% CI: 1.8,2.8)	Time to worsening of FACT-P score was delayed in 177Lu-PSMA-617+BSC/BSoC arm.

Title: Trial PSMA_617-01

VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)

	BPI-SF pain intensity scale (Median-time to improvement after worsening)	2.8 months	4.2 months	Time to improvement after worsening was faster in the 177Lu-PSMA-617+ BSC/BSoC arm: the ratio of the expected time to improvement following worsening in all randomized patients was 0.69 (95% CI: 0.54, 0.87, two-sided p<0.001).
	Time to BPI-SF pain intensity worsening (Median) (in PFS-FAS)	5.9 months (95% CI: 4.8,6.9)	2.2 months (95% CI: 1.8,2.8)	An estimated 48% reduction in risk of worsening (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the 177Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm. Time to worsening was delayed by 3.7 months in 177Lu-PSMA-617 +BSC/BSoC arm
	HE	NR	NR	NR
	Change in PSA (% to baseline) (Mean/Median) (in PFS-FAS)	-20.9/-68.6	50.4/24.3	The best percentage change from baseline in PSA, LDH and ALP levels all favor the 177Lu-PSMA-617+BSC/BSoC arm
	Change in LDH (% to baseline) (Mean/Median) (in PFS-FAS)	-23.1/-23.3	-9.2/-12.6	The best percentage change from baseline in PSA, LDH and ALP levels all favor the 177Lu-PSMA-617+BSC/BSoC arm
	Change in ALP (% to baseline) (Mean/Median) (in PFS-FAS)	-14.4/-17.0	0.6/-5	

Title: Trial PSMA_617-01 *VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)*	
Notes	Originally, the primary objective of this study was an arm-to-arm comparison of OS. In agreement with the FDA and shortly after study enrollment was initiated, the protocol was amended to implement alternate primary endpoints, meaning rPFS and OS designated as alternate primary endpoints. Because rPFS was a key secondary endpoint at the start of the study, data collection to support rPFS analysis as an alternate primary endpoint was already in place for all randomized patients. Based on this change, the statistical design of the study was such that, to be declared positive, the study would be required to reach statistical significance on either rPFS or OS at the respective allocated alpha level; it was not required to statistically meet both rPFS and OS to be declared a positive study. This was reasoned cy the observation that shortly after commencement of the trial, a high rate of withdrawal of consent in the BSC/BSoC only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that rPFS data could not be collected for these patients, which consequently could result in bias in the analysis of rPFS. As part of the plan to address the high rate of early withdrawal of consent in the BSC/BSoC only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 05-Mar-2019; therefore, rPFS was analyzed on an intent- to-treat (ITT) basis in these patients. The OS analysis was also planned on an ITT basis and included all randomized patients (i.e. including those randomized before 05-Mar-2019).

Title: Trial PSMA_617-01 *VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)*	
Analysis description	**Efficacy endpoints and overall type 1 error control** **Endpoint A: Radiographic progression-free survival*** **Prespecified final analysis:** Inferential test at α=0.004 (one-sided) *If **A** is positive* **Endpoint B: Overall survival*** **Prespecified final analysis:** Inferential test at α=0.025 (one-sided) *If **B** is positive* **Key secondary endpoints†** **Prespecified final analysis:** Inferential tests at α=0.05 (two-sided) **Other secondary endpoints** **Prespecified final analysis** Non-inferential tests at nominal α=0.05 (two-sided) *If **B** is not met* **Key secondary endpoints†‡** **Prespecified final analysis:** Non-inferential tests at nominal α=0.05 (two-sided) **Other secondary endpoints** **Prespecified final analysis:** Non-inferential tests at nominal α=0.05 (two-sided) *If **A** is not met* **B: Overall survival*** **Prespecified final analysis:** Inferential test at α=0.021 (one-sided) *If **B** is positive* Key secondary endpoints† Inferential tests at α=0.042 (two-sided) Other secondary endpoints Non-inferential tests at nominal α=0.05 (two-sided) *If **B** is not met§* Key secondary endpoints†‡ Non-inferential tests at nominal α=0.05 (two-sided) Other secondary endpoints Non-inferential tests at nominal α=0.05 (two-sided) *Alternate primary endpoints; study would be positive if either radiographic progression-free survival or overall survival were significant at allocated alpha on the prespecified log-rank test stratified by the randomization factors. †Key secondary endpoints were included in overall type 1 error control using Hochberg closed test procedure. ‡If overall survival is not met but radiographic progression-free survival is positive, the primary endpoint is met but key secondary endpoints are tested non-inferentially at nominal α=0.05 (two sided). §Primary endpoint not met if neither radiographic progression free survival nor overall survival is met. Source: [Study PSMA-617-01-Appendix 16.1.9]

Title: Trial PSMA_617-01 *VISION: An international, prospective, open label, multicenter, randomized Phase 3 study of ^{177}Lu-PSMA-617 in the treatment of patients with progressive PSMA-positive metastatic castration-resistant prostate cancer (mCRPC)*	
FINAL CONCLUSION.	The results of Study PSMA-617-01 demonstrated that treatment with 177Lu-PSMA-617 consistently resulted in statistically significant and clinically meaningful improvements in key measures of efficacy, including reduced risk of radiographic disease progression or death, a reduced risk of death, increased ORR and DCR, and delay in time to first SSE. Thus; the pivotal study PSMA-617-01 met its primary objectives for both alternate primary endpoints. Statistically significant improvements were demonstrated in favor of treatment with 177Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only also for all secondary endpoints listed.

2.6.5.3. Clinical studies in special populations

In the sub-study population of VISION (N=30), age in the study population was in the range of 52 to 80 years (median 67 years) and was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model; therefore, PK is not affected by age. In addition, no overall differences in efficacy were observed between patients ≥ 65 years of age and patients <65 years of age.

Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors.

No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted. After discussion it is now agreed that treatment with Pluvicto in patients with moderate renal impairment, specifically within the range of CLcr 30 to < 50 mL/min as well as in patients with severe renal impairment (CLcr < 30 mL/min) is not recommended. Treatment with Pluvicto would be allowed in patients with moderate renal impairment within the range of CLcr ≥ 50 to 59 mL/min, which reflects the inclusion criteria in Study PSMA-617-01.

Furthermore, the Post Marketing Requirement from FDA, Study CAAA617A12202 (CSR expected to be available in Q4 2026) is set to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of ^{177}Lu-PSMA-617 and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment.

It is expected that the study will provide additional information in this patient population leading to subsequent optimisation of the labelling recommendations.

As ^{177}Lu-PSMA-617 is not metabolized by, or primarily eliminated through, the liver (Kratochwil et al 2016), hepatic impairment is unlikely to significantly alter the PK of ^{177}Lu-PSMA-617. Hence, no dose adjustment is recommended or needed in patients with hepatic impairment.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

For diagnostic purposes PSMA was conjugated to gallium-68. This ^{68}Ga-PSMA-11 was used to determine patient eligibility based on PET imaging patterns defined by the central read criteria. Only patients with at least one PSMA scan-positive lesion identified on PSMA-PET/CT and no PSMA scan-negative lesion fulfilling the exclusion criteria were to be enrolled in the study, provided all other inclusion criteria were met. A total of 1003 patients underwent a ^{68}Ga-PSMA-11 PET/CT scan; 869

patients (86.6%) met the ^{68}Ga-PSMA-11 eligibility criteria to be enrolled in study. For more information regarding the analytical details and characteristics please refer to the Quality and PK sections.

There is sufficient external data that has demonstrated the validity of ^{68}Ga-PSMA-11 PET for localization of recurrent prostate cancer. Using blinded reads and independent lesion validation high PPV for ^{68}Ga-PSMA-11 PET, detection rate and interreader agreement for localization of recurrent prostate cancer is documented (Fendler et al., 2019). Moreover, the diagnostic tool used is under assessment in Europe too (parallel). Gozetotide after radiolabelling with gallium-68, is a radioactive diagnostic agent indicated for the identification of prostate specific membrane antigen (PSMA) positive lesions by positron emission tomography (PET) in adult patients with prostate cancer. (Details can be found in the Assessment reports of the parallel procedure EMEA/H/C/5488.)

However, it needs to be considered that on the basis of PSMA imaging alone 12.6% of the screened patients did not meet the eligibility criteria. Other studies, which assessed for PSMA heterogeneity by combining 18F-fluorodeoxyglucose (FDG) and gallium-68 (^{68}Ga)–labeled PSMA-11 scans performed with positron-emission tomography–computed tomography (PET–CT), identified a significantly higher percentage of patients in the mCRPC population (24 to 33%) harboured one or more FDG-positive, PSMA-negative lesions. Since in these patients the outcome with 177Lu-PSMA therapy was poor as compared with patients without such lesions (median overall survival, 6.0 months vs. 16.0 months; P<0.001) [Hindie, 2021] characterisation of the total tumour burden may be seen as suboptimal. However, considering the randomized trial design and the effect size of efficacy, it seems rather unlikely that this issue had a significant impact on trial outcome at the end.

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

Given the published data available at the time of PSMA-617-01 study inception, it was hypothesized that treatment with 177Lu-PSMA-617 plus best supportive care/best standard of care (BSC/BSoC) would provide therapeutic benefit for patients with mCRPC who had received at least 1 prior NAAD therapy and no more than 2 prior taxane-based chemotherapeutic regimens, and whose disease expressed PSMA as determined by a ^{68}Ga-PSMA-11 PET/CT scan.

To evaluate the PSMA-617-01 data in the context of available therapies in the intended patient population, publications describing the use of approved agents for mCRPC in the third-line treatment setting are summarized in Table 20. Acknowledging the pitfalls of cross-study comparisons, these published clinical studies indicate that treatment with 177Lu-PSMA-617 induces PSA reduction and radiologic response that may exceed the antitumor activity of all currently approved agents being used as third-line treatment.

Table 16: Efficacy summary of approved agents and 177Lu-PSMA-617 used as third-line treatment for mCRPC

Third-line treatment	number of patients included	OS median (months)	⩾50%[1] PSA Response (%)	PFS median (months)	ORR (by RECIST) (%)
Cabazitaxel[2]	594	12.3	32.3	4.5	21.6
Abiraterone acetate[3]	133	12.1	16.4	4.0	15.6
Enzalutamide[4]	696	9.7	19.4	3.5	9.3

Third-line treatment	number of patients included	OS median (months)	⩾50%[1] PSA Response (%)	PFS median (months)	ORR (by RECIST) (%)
Radium Ra-223 dichloride[5]	52	3.4[7]	-	-	-
Placebo (prednisone)[6]	346	9.8	2	-	-
	PSMA-617-01 VISION Prospective Study[8]				
177Lu-PSMA-617 +BSC/BSoC	**551**	**15.3**	**46.0[9]**	**5.9[9]**	**29.8[10]/51.1[11]**
BSC/BSoC Only	**280**	**11.3**	**7.1[9]**	**2.4[9]**	**1.7[10]/3.1[11]**

1 >50% response for enzalutamide, Thomsen et al (2014), Brasso et al (2015)
2 Pezaro et al (2014), Sella et al (2014), Al Nakouzi et al (2015), Caffo et al (2015), van Soest et al (2015), Kongsted et al (2016), de Wit et al (2019), Hofman et al (2021)
3 Loroit et al (2013), Noonan et al (2013), Caffo et al (2015)
4 Badrising et al (2014), Schmid et al (2014), Thomsen et al (2014), Azad et al (2015), Brasso et al (2015), Caffo et al (2015), Cheng et al (2015), Badrising et al (2016), Davies et al (2016)
5 Sidek et al (2018)
6 Smith et al (2016)
7 Mean
8 Not patient-weighted averages
9 PFS-FAS; ^{177}Lu-PSMA-617+BSC/BSoC (N = 385), BSC/BSoC only (N = 196)
10 Response evaluable analysis set; ^{177}Lu-PSMA-617+BSC/BSoC (N = 319), BSC/BSoC only (N = 120)
11 Response evaluable analysis set in patients with measurable disease at baseline; ^{177}Lu-PSMA-617+BSC/BSoC (N = 184), BSC/BSoC only (N = 64)

2.6.5.6. Supportive study(ies)

Not presented for efficacy, since the phase II trial PSMA-617-02 was evaluated for safety only.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

^{177}Lu-PSMA-617 has been developed as a PSMA-targeted RLT for patients with mCRPC.

Pivotal study

The pivotal phase 3 study VISION has a randomised, controlled design. This was supported at SA (EMA/CHMP/SAWP/221527/2019) which is agreed. Patients were randomized (2:1) to either ^{177}Lu-PSMA-617 + BSC/BSoC or BSC/BSoC only. For readability, however, the study arms are in this document referred to as (simply) the ^{177}Lu-PSMA-617 arm and the BSC/BSoC arm.

The study was open-label due to predicted toxicity in the experimental treatment arm and due to patient burden of radiation protection protocols in the control arm This can be agreed.

It is noted that the original version of the study protocol (dated 22-Mar-2018) underwent 3 global amendments. The resulting Protocol V4.0 is dated 08-Jul-2019. The first-patient first-visit was on 29-May-2018 and DCO is 27-Jan-2021.

Following SA, the Applicant as part of the VISION study conducted a sub-study in a non-randomized cohort of approximately 30 patients treated with ^{177}Lu-PSMA-617 at sites in Germany, to evaluate radiation dosimetry, PK, ECGs, safety and tolerability, and urinary metabolic stability. The protocol

amendment for including this sub-study (Protocol Amendment 4.1 dated 09-Aug-2019) was thus for Germany only. Patients in the sub-study were screened for eligibility, treated and followed-up similar to patients in the main study, but these patients were not included in the analyses of the randomized part of the study.

Patient population

Patients with progressive mCRPC who have previously received treatment with taxane chemotherapy and NAAD are limited to receiving BSC/BSoC intervention that is palliative in nature, but which does not increase their duration of survival. Progressive mCRPC was documented based on one or more of the following criteria as defined per PCWG3: serum PSA progression, soft-tissue progression, or progression of bone disease. Per the inclusion criteria, patients had received at least one NAAD (i.e. abiraterone acetate or enzalutamide) and at least one but no more than 2 previous taxane-based chemotherapy regimens. Thus, it is agreed that the included trial population represents an advanced mCRPC population and as reflected in the indication "for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy".

Regarding 'PSMA positivity' of the disease, patients underwent a ^{68}Ga-PSMA-11 PET/CT scan at screening and only patients with PSMA-positive mCRPC as determined by a central reader were included.

At SA, these criteria for definition of PSMA positivity were considered acceptable and using liver as 'comparator visual reference' was considered in accordance with general clinical practice and also acceptable. However, the criteria were deemed very strict, excluding every patient with (only) one relevant lesion not being PSMA-positive. A broader use in clinical practice after a potential MA was expected and it was, therefore, considered that the applied strict criteria would likely need to be reflected in the label. See below. It was also noted at SA that when at screening only a limited percentage of patients would present with a PSMA-negative status, a justification on the utility of the diagnostic test for the selection of patients would be required for the approval of ^{68}Ga-PSMA-11.

If a patient had received only one taxane regimen, the patient was eligible if the patient's physician deemed him unsuitable to receive a second taxane regimen (e.g., frailty assessed by geriatric or health status evaluation or intolerance, etc.). Originally, patients who were not willing to receive a second taxane regimen were also allowed to enrol, but with Protocol Amendment 2 (dated 01-Apr-2019 and resulting in Protocol V3.0) this was no longer allowed. This is reflected in section 5.1 of the SmPC. Also, it is noted that the second taxane regimen would normally be cabazitaxel, that is approved for mCRPC patients previously treated with a docetaxel-containing regimen (Jevtana SmPC), and that has shown a benefit in both rPFS and OS in the same disease setting (de Wit et al. N Engl J Med. 2019; Jevtana SmPC).

For inclusion, patients were required to have a life expectancy >6 months. Based on the Applicant clarification only 0.8% of the included patients in Study PSMA-617-01 did not meet the inclusion criteria of a life expectancy >6 months and only 3 of 1003 patients (0.3%) who were administered with did not meet this inclusion criterion. This information excludes a significant effect on the outcome.

Enrolled patients were randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus BSC/BSoC (investigational arm) or BSC/BSoC only (BSC/BSoC-only arm) using a permuted block scheme. This randomization ratio was used to provide more patients with a potential beneficial treatment over the existing therapies, which is agreed.

Randomization was stratified by 4 factors: LDH (≤260 IU/L vs. >260 IU/L); presence of liver metastases (yes vs. no); ECOG performance status score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no). However, in a multi-regional clinical trials, region (or country) should usually be a stratification factor. This was not considered. But a subgroup analysis by region (North America/Europe) was provided.

Dose selection

According to the Applicant, the selection of the ^{177}Lu-PSMA-617 dose and administration schedule in the VISION study was based on published clinical studies characterizing the safety and efficacy experience with ^{177}Lu-PSMA-617. Further, published radiation dosimetry studies, and a consideration of EBRT dose thresholds in organs at risk, provided some general guidance applied to cumulative radiation exposures. Lastly, experience with the since 2017 approved ^{177}Lu-radioligand therapeutic Lutathera (lutetium [^{177}Lu] oxodotreotide) provided class-based information. It is noted though, that the recommended dose regimen for Lutathera is 7.4 GBq Q8W for a total of four cycles (Lutathera SmPC), vs. (currently proposed) for ^{177}Lu-PSMA-617 the same dose but Q6W and for 6 cycles. The selected dose of 7.4 GBq Q6W for 6 cycles was intended to maximize the probability of efficacy, while maintaining safety parameters which are appropriate for the patient population.

Of note, after four cycles of ^{177}Lu-PSMA-617 treatment the investigator had to determine whether the patient: 1) showed evidence of response; 2) had signs of residual disease; and 3) had tolerated treatment well. If the patient met all three criteria, then treatment could be continued up to 6 cycles.

In CHMP scientific advice, it was recommended to evaluate the feasibility of pre-specified subgroup analyses on patient and/or lesion level based on the level of PSMA expression. However, information on this matter was not provided, consequently, no firm conclusions can be drawn. This could have been important information, as very recently in a multicentre, retrospective study tumour PSMA expression and the number of PSMA-positive metastatic lesions were (amongst other factors) predictors for OS after ^{177}Lu-PSMA-617 treatment (Gafita et al. Lancet Oncol. 2021). Patients in the investigational arm received either 7.4 GBq (±10%) 177Lu-PSMA-617 once every 6 weeks (±1 week) for up to 6 cycles (a maximum of 6 cycles) plus BSC/BSoC. This posology was based on clinical experience with Lutathera and previous clinical studies using 177Lu-PSMA considering dosimetry results. It reflects the intention to select a high dose regime to achieve the best efficacy outcome and reveals a significant dose escalation compared with the previous experience, combining a high dose, a more intensive treatment with shorter recovery periods and more cycles than previous experience. Insofar, it seems likely that safety risk are increased compared with published trials using lower number of treatment cycles and/or doses. Previous trials with 177-Lu-PSMA recommended only a dose of 4 cycles of 6 GBq every 8 weeks and the German Society of Nuclear Medicine even recommended a lower dose of 6.0 GBq dose together with a longer recovery time of 8 weeks for a maximum of 3 cycles only (Fendler et al 2016). The reasons for this caution are clearly safety concerns. However, according to the available data from external sources in the literature, only the TEAEs dry eyes and diarrhoea seemed to be more pronounced (>10% difference) with the higher dose, thereby confirming a higher off-target toxicity. However, the reliability of the external data from different trials remains limited due to methodological issues.

Moreover, it is also acknowledged that in the recently published, phase 2 TheraP study in 200 mCRPC patients (Hofman et al. Lancet. 2021), that compared ^{177}Lu-PSMA-617 against cabazitaxel, ^{177}Lu-PSMA-617 was also given Q6W and for up to 6 cycles. The starting dose was 8.5 GBq ^{177}Lu-PSMA-617 and reduced by 0.5 GBq per cycle, adding up to a cumulative dose of up to 43.5 GBq. This dose is similar to the maximum cumulative dose of 44.4 GBq in the VISION study. In the TheraP study, 46% of the patients who were treated with ^{177}Lu-PSMA-617 completed protocol therapy and the

median number of cycles was five (IQR 3–6). Dose reductions were documented in 12 men treated with ^{177}Lu-PSMA-617, but treatment was discontinued because of toxicity in only one patient (1%). In the TheraP study, treatment with ^{177}Lu-PSMA-617 seemed to be tolerated well using a dose regimen that adds up to a cumulative dose similar to in the VISION study.

The current posology, which recommends treatment regimen for ^{177}Lu-PSMA-617 for a total of 6 cycles (doses) of 7.4 GBq administered intravenously every 6 weeks (± 1 week) is a significant dose escalation compared with the previous experience, including a high dose, more intensive treatment with shorter recovery periods and more cycles than previous experience. Although it is acknowledged that the trial was very successful, it needs also to be considered that the radiation-related off-target toxicity was obviously higher than in other trials.,

In conclusion, the choice for the dose regimen in the VISION study is acceptable, even though it is noted that there have been no randomised controlled prospective studies with ^{177}Lu-PSMA-617 in patients with mCRPC comparing safety and efficacy of various dose ranges, cycle intervals and number of cycles. See the safety section of this AR for discussion on whether there may be a potential for ameliorated tolerability at a lower dose level.

Comparator

BSC/BSoC for each patient was selected and optimized at the discretion of the patient's physician prior to randomization, and was administered as per the physician's discretion and protocol at the institution. BSC/BSoC therapy included amongst other things ADT, any NAAD (e.g. enzalutamide, abiraterone, apalutamide), other hormonal agents, corticosteroids, radiation in any external beam or seeded form, and bone-targeted agents (e.g. zoledronic acid, denosumab, bisphosphonates). It excluded investigational agents (e.g. olaparib that was investigational at the time), cytotoxic chemotherapy (e.g. cabazitaxel), immunotherapy, and other systemic radiopharmaceuticals (e.g. 223Ra-dichloride).

At SA, it was fully acknowledged that no clear evidence-based treatment recommendations can be given in advanced mCRPC patients that have already been treated with NAAD and taxane-containing chemotherapy. Based on this, the BSC/BSoC comparator was considered acceptable. This still holds true. It is noted though, that in 2020 olaparib was approved for a subset of the VISION study population, i.e. patients with mCRPC and *BRCA1/2*-mutations who have progressed following prior therapy that included a NAAD (Lynparza SmPC).

Endpoints

The efficacy population (FAS) comprised 831 randomized patients in Study PSMA-617-01 with mCRPC: 551 patients were randomized to ^{177}Lu-PSMA-617 (i.v. 7.4 GBq (±10%) once every 6 weeks (±1 week) for a maximum of 6 cycles) plus BSC/BSoC (investigational arm) and 280 patients were randomized to BSC/BSoC only (control arm). As of the data cut-off date of 27-Jan-2021, the median study follow-up was 20.9 months.

Originally, the primary objective of this study was an arm-to-arm comparison of OS. Shortly after study enrollment was initiated, the protocol was amended to implement alternate primary endpoints, meaning rPFS and OS designated as alternate primary endpoints. In the original protocol rPFS was included at the start as the first key secondary endpoint. On February 2019, 44 of 61 patients randomized to the control arm had withdrawn consent prior to the first post-baseline radiological assessment (Week 8). This meant that rPFS data could not be collected for these patients, which consequently could result in bias in the analysis of rPFS. In consequence, the Sponsor initiated a set of corrective actions in study conduct at the sites to mitigate this risk, which concerned mainly the

primary objective and the primary endpoint of the trial as detailed in amendment 2 (dated 1. April 2019). In this amendment, the primary objective and the primary endpoint of Study PSMA-617-01 was changed from OS only to two alternate primary endpoints. The previous key secondary endpoint radiographic PFS, assessed by blinded independent central review (BICR), was added as a second component to the alternate primary endpoints (OS and rPFS).

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

Because rPFS was a key secondary endpoint at the start of the study, data collection to support rPFS analysis as an alternate primary endpoint was already in place for all randomized patients. Based on this change, the statistical design of the study required to reach statistical significance on either rPFS or OS at the respective allocated alpha level to become positive. To minimize the potential for bias in the analysis of rPFS due to the differential withdrawal of consent rate between the two treatment arms, only patients randomized after full implementation of enhanced study site education measures (05-Mar-2019) were to be included in the confirmatory/primary analysis of rPFS, the allocation of alpha between rPFS and OS was adjusted to allow for analysis of fewer rPFS events while still maintaining the original power for both rPFS and OS, and the total number of patients randomized in the study was increased to ensure sufficient events to maintain power.

Statistical methods

It is noted that the original version of the SAP is dated 08-Jun-2018, Version 2.0 is dated 24-Oct-2019, and Version 3.0 is dated 18-Jan-2021. The last date is only a few days before the DCO for the open-label VISION study, i.e. 27-Jan-2021.

The approach to use the alternate primary endpoints is deemed justified and was agreed in a SAWP advice considering the ICH E9 Guideline "Statistical Principles for Clinical Trials" (EMA 1998), as well as in the EMA "Guideline on multiplicity issues in clinical trials" (EMA 2017). This detailed that when using alternate primary endpoints, although demonstration of a treatment effect on at least one of the 2 primary endpoints is sufficient, results for all of the prespecified primary endpoints (rPFS and OS in this case), both positive and negative, are considered in the overall assessment of risks and benefits.

However, it was clarified in the advice that the OS analysis should still include all randomized patients from the start of the study (EMA Scientific Advice 2019) and therefore allows additionally a valid analysis of the initial primary endpoint OS only.

With respect to methodical aspects, it needs to be considered that the statistical analysis plan was not finalized before the beginning of this open-label study, however, the analyses described in the SAP are consistent with the ones in the study protocol and changes to study design (primary endpoint, analysis populations) were not critical for study success. It is agreed that the changes maintained all of the assumptions of clinical benefit on which the study was originally powered. The pre-specified multiplicity strategy provided adequate control of the family-wise type 1 error rate for the primary endpoints and key secondary endpoints.

The censoring rules for rPFS were generally in line with the relevant EMA guideline (CHMP/27994/2008 Rev. 1) besides censoring of patients with two consecutive missed tumour assessments immediately prior to event. A sensitivity analysis considering these patients as events was provided; however, as

more additional categories of rPFS events were also introduced in this analysis, it is also not identical with the EMA-preferred analysis.

As a result of the corrective actions, withdrawal of consent from treatment with BSC/BSoC subsequently decreased from 28.6% to 11.2%.

As frequently in trials comparing an investigational product with BSC/BSoC, duration of exposure to randomized treatment for the 2 randomized arms was significantly shorter in the BSC/BSoC arm (Median: PSMA: 7.8 months vs BSC only: 2.1 months).

Key secondary endpoints after amendment 2 included an arm-to-arm comparison of ORR and DCR as measured by RECIST v1.1, as well as time to first symptomatic skeletal event (SSE). Secondary endpoints have been defined by PCWG3 as well as FDA and EMA guidance. It is agreed that these endpoints are clinically meaningful and informative in order to provide evidence regarding the roboustness of the trial outcome.

Similarly, the additional secondary endpoints including PFS (radiographic, clinical, or PSA progression), biochemical response as measured by change over time in PSA, PSA doubling time, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), PSA response and duration of PSA response are assessed as clinically relevant and may indicate robustness of outcome.

In view of the highly symptomatic nature of advanced mCRPC both validated pain measurements (the BPI-SF) and HRQoL measurements (the EQ-5D-5L and the FACT-P) were collected using various questionnaires. In conclusion, all secondary endpoints used are acceptable and generally fully in accordance with PCWG3 as well as FDA and EMA guidance recommendations.

Although the applicant's justification that the change to implement alternate primary endpoints does not negatively affect the OS endpoint and full integrity was maintained for this endpoint and for the study may be correct, additional clarification regarding this issue was requested both, from a methodological and clinical point of view. From the submitted details and additional explanations it is agreed that, the overall reliability of the data is not further challenged since the change in population before and after the amendment differs even in a worst case analysis would not have led to imbalances in prognosis.

The ongoing COVID-19 pandemic had minimal impact on this study, since enrolment was completed on 23-Oct-2019 (prior to the beginning of the pandemic in Europe and North America), and the last dose of 177Lu-PSMA-617 was administered on 26-Jun-2020. Due to the COVID-19 pandemic, changes to the conduct of this study were implemented to ensure the safety and well-being of study participants, and to enable trial oversight and compliance with the study protocol. Six patients discontinued 177Lu-PSMA-617 due to the pandemic, and they all had already received at least 4 cycles of study drug. Missed assessments or procedures due to the pandemic were estimated to represent less than 0.25% of the data to be collected and 3 deaths were related to COVID-19 infections. Based on results of sensitivity analyses presented to assess the impact of the COVID-19 pandemic on the evaluation of the alternate primary endpoints, it is agreed that the pandemic had no relevant impact on the alternate primary efficacy endpoint evaluations (data not shown).

Efficacy data and additional analyses

The pivotal trial PSMA-617-01 has shown convincing and roboust evidence that treatment with ^{177}Lu-PSMA-617 leads to a statistically significant and clinically meaningful improvements in key measures of efficacy in the intended target population.

With respect to the alternate primary endpoint it is noted that –although not essentially needed – both endpoint component were highly statistically significant (p< 0.001) in favour for patients treated with with 177Lu- PSMA-617+BSC/BSoC relative to BSC/BSoC only. Roboustness is indicated by statistically high significant differences in favour for the 177Lu-PSMA-617+BSC/BSoC arm compared with BSC/BSoC alone arm for all key secondary as well as the additional secondary endpoints selected.

For rPFS, there was an estimated 60% risk reduction of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57; stratified log-rank test p < 0.001, one-sided) and median rPFS was prolonged by 5.3 months, from 3.4 months (99.2% CI: 2.4, 4.0) in the BSC/BSoC only arm to 8.7 months (99.2% CI: 7.9, 10.8) in the 177Lu-PSMA-617+BSC/BSoC arm. The presented results of sensitivity analyses for rPFS as well as an additional analysis of rPFS based on the FAS was also supportive of the primary analysis were supportive for the primary analysis result. Moreover, an rPFS improvement of five months may allow presuming some improvement in quality of life for patients also. However, since the return rate of the PRO questionnaires was extremely limited (11%), this effect is not sufficiently reliable to be confirmative. Nevertheless, it is noted that in difference to other approved mCRPC therapies, such as radium-223, also a rPFS benefit was documented in addition to increased overall survival.

Similarly, for OS, a statistically significant and clinical relevant estimated 38% risk reduction of death (HR =0.62; 95% CI: 0.52, 0.74; stratified log-rank test p < 0.001, one-sided) was observed. This correlates to a prolongation in median OS of 4.0 months, from 11.3 months (95% CI: 9.8, 13.5) in the BSC/BSoC only arm to 15.3 months (95% CI: 14.2, 16.9) in the177Lu-PSMA-617+BSC/BSoC arm.

With respect to the changes performed in the efficacy evaluation and the change of the primary endpoint OS only to an alternative endpoint consisting of rPFS and OS, the results of a supplementary OS analysis based on the first 750 patients randomized in the FAS are reassuring. This approach mimics the OS analysis as planned in the initial protocol and resulted -consistently with the primary analysis results- to an HR of 0.63 (95% CI: 0.52, 0.77) favoring the 177Lu-PSMA-617+BSC/BSoC arm (stratified log-rank test p < 0.001, one-sided) in a similar range again. Furthermore, an additional OS analysis conducted on the PFS-FAS was consistent with and supportive of the primary analysis (HR = 0.63; 95%CI, 0.51, 0.79; stratified Log-rank test p < 0.001, one-sided).

However, it needs to be considered that the difference between both arms in trial PSMA-617-01 was in the same range as observed in other controlled clinical trials in the mCRPC target population (Radium-223 vs BSoC, ALSYMPCA trial : 3.6 months or Olaparip vs Abi/Enza, PROfound trial : 3.4 months). Insofar, in the advance mCRPC population the treatment option with 177-Lu-PSMA is seen as important, although not dramatically changing the fate of the patient. However, this was also not expected.

Results of analyses performed to assess sensitivity of rPFS and OS to censoring due to drop-outs were in general fully consistent with and supportive of the primary analysis results and may allow to presume that the initial high drop-out rate had no impact on the interpretation or robustness of the primary analysis results. Similarly, homogeneity and consistency of the alternate primary endpoints rPFS and OS were also evident across subgroups, including the baseline stratification factors, age, region, baseline PSA, prior therapies, and concurrent therapies, demonstrating a consistent ^{177}Lu-PSMA-617 treatment effect. The only exception was subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and baseline PSADT >9 months).

From a methodical point of view, it is appreciated that sensitivity analyses were pre-specified addressing the influence of censoring rules and definition of rPFS events, and that additional analyses on the influence of COVID-19 were conducted. Considering the (non-differential) drop-out with early

withdrawals of consent in the control arm, additional analyses were provided for OS and rPFS (both for PFS-FAS and FAS).

Also reverse Kaplan-Meier curves (i.e. reversing event and censoring) were provided and additional Cox regression analyses adjusting for additional covariates (reasons for trial discontinuation) were conducted. It was clarified that differential censoring occurred for OS, which was mainly due to ~10% early drop-outs in the control arm (probably explained by the issue with withdrawal of consent) while no further differentiation occurred during later follow-up.

For rPFS, it was already known that considerable early differential drop-out occurred as this was the reason for introducing corrective actions and re-defining the primary analysis population for the rPFS analysis. However, there was still considerable early drop-out in the PFS-full analysis set (> 20% censoring at time 0, with further differentiation after 2 months, i.e. first PFS assessment time point).

In summary, the panel of additional analyses convincingly demonstrated that differential drop-out had no critical influence on the conclusions from the study.

The study met also all key secondary efficacy objectives, with highly statistically significant improvements in favor of treatment with 177Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only.

At SA, it was advised to evaluate the feasibility of pre-specified subgroup analyses on patient and/or lesion level based on the level of PSMA. The Applicant performed a pre-planned, exploratory quantitative analysis to assess the association of baseline ^{68}Ga-PSMA-11 PET/CT parameters with rPFS, OS, and other efficacy endpoints only on the patients randomized to the ^{177}Lu-PSMA-617 treatment arm. This is not (fully) understood and is regrettable, as the quantitative analysis thus only considers prognostic factors for efficacy outcomes under ^{177}LuPSMA-617 + BSC/BSoC treatment, rather than predictive factors for improved efficacy relative to BSC/BSoC alone. Therefore, no firm conclusions can be drawn. It would have been preferred to include (scans of) patients from both treatment arms in the quantitative analysis to potentially identify subgroups of patients that benefit more from adding ^{177}LuPSMA-617 to BSC/BSoC.

As the nature of any additional analysis/analyses will also be exploratory and moreover, *post hoc*, the results thereof are unlikely to (significantly) impact the benefit-risk assessment.

Although the reliability of PRO-outcome in an open trial design may be challenged, it should be noted that also results in favor of treatment with 177Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only were also observed for PROs, indicating patient stabilization/slower deterioration while on treatment. FACT-P total score showed an estimated 46% reduction in risk of worsening, clinical progression or death (HR = 0.54; 95% CI: 0.45, 0.66; Cox two-sided p-value: < 0.001) in the 177Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm and BPI-SF pain intensity scale showed that time to worsening was delayed by 3.7 months in 177Lu-PSMA-617+BSC/BSoC arm compared to BSC/BSoC only arm.

With respect to efficacy in special populations, age in the trial was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model; claiming that PK is not affected by age. In addition, no overall differences in efficacy were observed between patients ≥ 65 years of age and patients <65 years of age.

Treatment with Pluvicto in not recommended in patients with renal impairment with baseline CLcr < 50 mL/min. Treatment with Pluvicto in patients with renal impairment within the range of CLcr ≥ 50 to 59 mL/min is acceptable. This recommendation is in accordance with the Study PSMA-617-01 inclusion criterion #14.c.

Furthermore, it needs to be considered that the presented subgroup analyses have shown that only 6.6% of Black/African American and only 2.4 % Asians were included. Considering that the highest death rate in Prostate cancer is observed in Black/African Americans, this limitation is important.

Most relevant, external data from other trial in PSMA-positive mCRPC who progressed standard therapies, including antiandrogen therapies (abiraterone, enzalutamide or both) and taxane based chemotherapy (docetaxel or cabazitaxel), or who were not eligible for chemotherapy is available. These data show consistency with respect to the results of Study PSMA-617-01 and thereby reliably confirm the clinical relevant benefit as reported from the here discussed pivotal trial.

Since metastatic castration-resistant prostate cancer does not occur in a paediatric population, and there are no other indications known at this time that are likely to benefit a product specific waiver was granted and no specific considerations for the paediatric population are seen.

Supportive study

The supportive phase 2 study PSMA 617-02 (RESIST-PC; NCT03042312) was a prospective, open-label study to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 and was conducted at 2 treatment centres. This study enrolled patients with progressive, PSMA-positive mCRPC previously treated with ≥ 1 NAAD and who were either taxane-naive or taxane pre treated. Enrolled patients were randomized to one of two 177Lu-PSMA-617 treatment doses, i.e. 6.0 GBq (± 10%) or 7.4 GBq (± 10%) every 8 ± 1 weeks until reaching 4 cycles (or threshold maximum dose to the kidneys of 23 Gy). Patients were able to receive BSC/BSoC during the study. The primary objectives of the study were 1) to assess the clinical safety of ^{177}Lu-PSMA-617; and 2) to assess the efficacy as defined by proportion of patients with PSA response ≥ 50% decline at 12 weeks from baseline. In total, 200 patients were scheduled to be enrolled.

However, enrolment was terminated early by the study Sponsor, since the study was not consistent with the overall strategy of the company. Due to only limited PSA data being available for the number of actual patients enrolled being 71, the efficacy endpoints were not analysed as planned in the protocol. The only efficacy analyses performed using the limited data available were for clinicaltrials.gov, as this website requires all available data for primary and secondary endpoints to be disclosed. It is agreed with the Applicant that there was insufficient data to draw reliable conclusions. Therefore, no efficacy results of the supportive study RESIST-PC will be discussed here. This study is only providing supportive safety data in this application, see the safety section of this AR.

Wording of indication

The Applicant originally proposed the following indication:

"*^{177}Lu-PSMA-617 is indicated for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy.*"

According to (the most) recent EMA guidance (EMA/CHMP/483022/2019) there is a need to specify in the indication wording whether Pluvicto should be used as monotherapy or in combination with other products. Considering that in the VISION study ^{177}Lu-PSMA-617 treatment was given in combination with BSC/BSoC, with castration as essential backbone thereof englobed as "androgen deprivation therapy (ADT)" that also encompasses surgical castration, and that androgen receptor (AR) pathway inhibition was not mandatory, the indication was agreed to be updated to reflect that ^{177}Lu-PSMA-617 is indicated in combination with ADT with or without AR pathway inhibition.

2.6.7. Conclusions on the clinical efficacy

In the pivotal study VISION, treatment with ^{177}Lu-PSMA-617 showed an improvement in both primary endpoints of rPFS by BICR and OS compared with treatment with BSC/BSoC, of which the OS benefit is considered clinically relevant. The OS data/results are considered sufficiently mature for B/R assessment and are considered robust, as all performed sensitivity/supportive analyses support the OS primary analysis and all subgroup analyses for OS provided results consistent with this analysis.

The rPFS result and the results for the key secondary endpoints (ORR, DCR, and SSE) are considered to provide support for the OS result.

The final wording of the indication was updated to reflect that ^{177}Lu-PSMA-617 is indicated in combination with ADT with or without AR pathway inhibition.

2.6.8. Clinical safety

Safety data for ^{177}Lu-PSMA-617was provided derived from the two studies PSMA-617-01 (pivotal) and PSMA-617-02 (supportive).

Pivotal (Main source of safety information)

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

Supportive

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

2.6.8.1. Patient exposure

Recommended Posology:

The recommended dose for ^{177}Lu-PSMA-617 is 7 400 MBq (200 mCi) every 6 weeks (±1 week) for a total of 6 doses.

Duration of exposure

Duration of exposure was longer and the mean/median number of cycles started by the patients were higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm due to the longer time spent on the study by patients randomized to this arm.

An overview of the duration of exposure to randomized treatment for the 2 randomized arms is provided in Table 21.

Table 17: Duration of exposure to randomized treatment (FAS Safety Analysis Set) in the PSMA-617-01 study

	177Lu-PSMA-617 +BSC/BSoC N=529	**BSC/BSoC only N=205**

Duration of exposure (months)		
Mean (SD)	**7.9 (4.3)**	3.5 (3.9)
Median	**7.8**	2.1
Min-Max	0.3-24.9	0.0-26.0
Less than 3 months	71 (13.4)	140 (68.3)
At least 3 months	458 (86.6)	65 (31.7)
At least 6 months	320 (60.5)	26 (12.7)
At least 9 months	167 (31.6)	16 (7.8)
At least 12 months	88 (16.6)	9 (4.4)
At least 15 months	31 (5.9)	6 (2.9)
At least 18 months	15 (2.8)	4 (2.0)
At least 21 months	3 (0.6)	1 (0.5)
At least 24 months	2 (0.4)	1 (0.5)

Source: [Study PSMA-617-01-Table 14.3.5.2.1]. [CHMP Day 120 Appendix Q84-Table 8.11.3b]
Data Cutoff Date: 27JAN2021

An overview of duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles for patients randomized to 177Lu-PSMA-617+BSC/BSoC only arm in the PSMA-617-01 are shown in Table 22.

Table 18: Duration of ^{177}Lu-PSMA-617 exposure in PSMA-617-01 and summary of cycles (FAS Safety Analysis Set)

	177Lu-PSMA-617 +BSC/BSoC N=529
Duration of exposure (months)	
Mean (SD)	**6.3 (2.4)**
Median	**6.9**
Min-Max	0.3-10.2
Number of cycles started by patient	
Mean (SD)	4.5 (1.7)
Median	5.0
Min-Max	1-6
Number of cycles started by patient, n (%)	
1 cycle	33 (6.2)
2 cycles	57 (10.8)
3 cycles	81 (15.3)
4 cycles	69 (13.0)
5 cycles	43 (8.1)
6 cycles	246 (46.5)
Average duration of treatment cycles (months)	
Mean (SD)	1.4 (0.1)
Median	1.4
Min-Max	0.3-2.4
Patients with at least one cycle delayed, n (%)	93 (17.6)
Number of cycles delayed	
N	93
Mean (SD)	1.2 (0.5)
Median	1.0
Min-Max	1-3
Reason for delay of cycle(s)[1], n (%)	
Delayed due to scheduling purposes	56 (10.6)
Delayed due to AE	40 (7.6)
Overall extent of 177Lu-PSMA-617 exposure	
Cumulative dose (GBq)	
Mean (SD)	33.4 (12.8)
Median	37.5
Min-Max	7.0-48.3
Dose intensity (GBq/month)	

	177Lu-PSMA-617 +BSC/BSoC N=529
Mean (SD)	5.5 (1.2)
Median	5.5
Min-Max	3.1-25.3
Relative dose intensity (%)	
Mean (SD)	104.5 (21.9)
Median	102.6
Min-Max	90.5-471.3

[1]n=93
A patient may be counted in more than one row for reason for delay of cycle. 177Lu-PSMA-617 cycles are once every 6 weeks for a maximum of 6 cycles.
Source: [Study PSMA-617-01–Table 14.3.5.2.1.1], [Study PSMA-617-01–Table 14.3.5.5.1]

2.6.8.2. Adverse events

The following Table 23 provides an overview about the general safety profile of ^{177}Lu-PSMA-617 compared to BSC/BSoC from the adverse events observed in the FAS of trial PSMA-617-01:

Table 19: Overview of TEAEs during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

Type of Safety event	177Lu-PSMA-617+BSC/BSoC N=529	BSC/BSoC only N=205 n (%)
TEAE	519 (98.1)	170 (82.9)
Serious TEAE	192 (36.3)	57 (27.8)
Grade 3/4/5 TEAE	**279 (52.7)**	**78 (38.0)**
Drug-related TEAE	**451 (85.3)**	**59 (28.8)**
Serious drug-related TEAE	**49 (9.3)**	5 (2.4)
Drug-related grade 3/4/5 TEAE	**150 (28.4)**	8 (3.9)
TEAE leading to reduction of ^{177}Lu-PSMA-617	30 (5.7)	0
TEAE leading to reduction of BSC/BSoC	17 (3.2)	7 (3.4)
TEAE leading to interruption of ^{177}Lu-PSMA-617	85 (16.1)	2 (1.0)[1]
TEAE leading to interruption of BSC/BSoC	50 (9.5)	14 (6.8)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	63 (11.9)	1 (0.5) [1]
TEAE leading to discontinuation of BSC/BSoC	45 (8.5)	16 (7.8)
Fatal TEAE	19 (3.6)	6 (2.9)

Drug-related is related to any study drug (^{177}Lu-PSMA-617 or BSC/BSoC) as assessed by the investigator.

[1] Four patients randomized to 177Lu-PSMA-617+BSC/BSoC arm received BSC/BSoC only, and therefore contribute to the FAS safety analysis set of the BSC/BSoC arm, see [Study PSMA-617-01-Section 10.1.2]. Source: [Study PSMA-617-01-Table 14.3.2.1]

TEAEs were usually more frequent in the 177Lu-PSMA-617+BSC/BSoC arm than in BSC/BSoC only arm for all categories (except TEAEs leading to reduction of BSC/BSoC).

As shown in the Table 23above, the differences were more pronounced for the drug-related TEAEs (85.3% patients vs. 28.8% patients), drug-related grade 3/4/5 TEAEs (28.4% patients vs. 3.9% patients), and grade 3/4/5 TEAEs (52.7% patients vs. 38.0% patients). Serious drug related TEAEs

were more than threefold higher in patients exposed to 177Lu-PSMA-617+BSC/BSoC. Insofar, the treatment has clearly a higher risk than BSC/BSoC alone.

TEAEs reported with respect to primary SOC and maximum grade in PSMA-617-01 are presented in Table 24 during randomized treatment.

Table 20: TEAEs during randomized treatment regardless of study treatment relationship by primary system organ class in PSMA-617-01 (FAS Safety Analysis Set)

	177Lu-PSMA-617+BSC/BSoC		**BSC/BSoC only N=205**	
System organ class	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at least one event	**519 (98.1)**	**279 (52.7)**	**170 (82.9)**	**78 (38.0)**
Gastrointestinal disorders	*399 (75.4)*	*31 (5.9)*	*65 (31.7)*	*6 (2.9)*
General disorders and administration site	324 (61.2)	50 (9.5)	79 (38.5)	10 (4.9)
Musculoskeletal and connective tissue disorders	311 (58.8)	48 (9.1)	83 (40.5)	15 (7.3)
Blood and lymphatic system disorders	*253 (47.8)*	*127 (24.0)*	*37 (18.0)*	*14 (6.8)*
Metabolism and nutrition disorders	222 (42.0)	33 (6.2)	61 (29.8)	9 (4.4)
Nervous system disorders	184 (34.8)	37 (7.0)	55 (26.8)	17 (8.3)
Infections and infestations	167 (31.6)	56 (10.6)	33 (16.1)	9 (4.4)
Respiratory, thoracic and mediastinal disorders	142 (26.8)	22 (4.2)	39 (19.0)	8 (3.9)
Investigations	125 (23.6)	15 (2.8)	31 (15.1)	3 (1.5)
Renal and urinary disorders	*106 (20.0)*	*36 (6.8)*	*32 (15.6)*	*8 (3.9)*
Injury, poisoning and procedural complications	98 (18.5)	17 (3.2)	24 (11.7)	6 (2.9)
Vascular disorders	84 (15.9)	29 (5.5)	28 (13.7)	6 (2.9)
Skin and subcutaneous tissue disorders	69 (13.0)	0	12 (5.9)	0
Psychiatric disorders	67 (12.7)	8 (1.5)	22 (10.7)	2 (1.0)
Eye disorders	53 (10.0)	6 (1.1)	9 (4.4)	0
Cardiac disorders	25 (4.7)	11 (2.1)	6 (2.9)	3 (1.5)
Reproductive system and breast disorders	17 (3.2)	2 (0.4)	0	0
Ear and labyrinth disorders	16 (3.0)	0	3 (1.5)	0
Neoplasms benign, malignant and unspecified	15 (2.8)	4 (0.8)	2 (1.0)	1 (0.5)
Hepatobiliary disorders	13 (2.5)	5 (0.9)	8 (3.9)	3 (1.5)
Endocrine disorders	8 (1.5)	1 (0.2)	2 (1.0)	1 (0.5)
Surgical and medical procedures	4 (0.8)	2 (0.4)	0	0
Congenital, familial and genetic disorders	1 (0.2)	1 (0.2)	0	0
Product issues	1 (0.2)	1 (0.2)	0	0
Immune system disorders	0	0	1 (0.5)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.1]

The **greatest differences (≥20%) between the 2 treatment arms** (177Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were observed for:

- Gastrointestinal disorders: 75.4% patients versus 31.7% patients
- General disorders and administration site conditions: 61.2% patients versus 38.5% patients
- Blood and lymphatic system disorders: 47.8% patients versus 18.0% patients

The **greatest differences (≥10%) in the incidence of TEAEs according PT between the 2 treatment arms** (177Lu- PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were observed for:

- Fatigue: 43.1% patients versus 22.9% patients
- Dry mouth: 38.8% patients versus 0.5% patients
- Nausea: 35.3% patients versus 16.6% patients
- Anemia: 31.8% patients versus 13.2% patients
- Diarrhea: 18.9% patients versus 2.9% patients
- Vomiting: 18.9% patients versus 6.3% patients
- Thrombocytopenia: 17.2% patients versus 4.4% patients
- Lymphopenia: 14.2% patients versus 3.9% patients
- Leukopenia: 12.5% patients versus. 2.0% patients
- Urinary tract infection: 11.0% patients versus 1.0% patients

Overall, **high grade TEAEs (grade ≥3) were reported as relatively infrequent** (<5.0% patients) in both arms, except for the following events which were more frequent in the 177Lu-PSMA-617+BSC/BSoC arm versus the BSC/BSoC only arm:

- **anemia** (12.9% patients vs. 4.9% patients),
- **thrombocytopenia** (7.9% patients vs.1.0% patients),
- **lymphopenia** (7.8% patients vs. 0.5% patients), and
- **fatigue** (5.9% patients vs. 1.5% patients).

These grade ≥ 3 AEs of the blood and lymphatic system and fatigue were anticipated for ^{177}Lu- PSMA-617 considering the administration of therapeutic levels of the radioactive compound in these patients with advanced cancer. It may be noted that though these events were more frequent as expected with this treatment (occurring in the range of 6-13% frequency, approximately), they only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤3.0% of patients.

In conclusion, the safety outcome could be expected to some degree for ^{177}Lu-PSMA-617 therapy from available external literature data and these events reflect known toxicities from the radiation resulting from ^{177}Lu-PSMA-617 treatment. In general, the TEAEs fully reflect the locations characterised as relevant off-targets. No new or unexpected safety concern was raised during treatment with ^{177}Lu-PSMA-617 in the PSMA-617-01 study.

Adverse events of special interest:

From the data in literature ^{177}Lu-PSMA-617 is already known to increase risk of Fatigue, Dry mouth, Myelosuppression (including anemia, thrombocytopenia, lymphopenia, leukopenia), Nausea and Vomiting, and Renal effects. It is acknowledged that all these AESI can be attributed to the mechanism of action of ^{177}Lu-PSMA-617 or can be associated with active anti-cancer treatment.

Fatigue event is frequent in an advanced cancer population per se; however, this TEAE was clearly more frequently reported in the 177Lu-PSMA-617+BSC/BSoC arm (49.1% patients) as compared to the BSC/BSoC only arm (29.3% patients). Since event probability estimates show also a higher probabilities of fatigue in the 177Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm, this is

clearly a safety risk associated to the radiation treatment. However, events of fatigue leading to withdrawal of ^{177}Lu-PSMA-617 were infrequent (0.4%).

Myelosuppression: The frequency of myelosuppression related events (including anemia, thrombocytopenia, lymphopenia, leukopenia) was **higher in the 177Lu-PSMA-617+BSC/BSoC arm (47.4% patients)** as compared to the **BSC/BSoC only arm (17.6% patients)**. Similarly, high grade (≥3) events of myelosuppression were higher in the 177Lu-PSMA-617+BSC/BSoC arm (23.4% patients vs. 6.8% patients), as were the SAEs (5.1% patients vs. 0.5% patients).

Myelosuppression related events leading to withdrawal of ^{177}Lu-PSMA-617 were frequent (7.0% patients). Event probability estimates show clearly higher probabilities of myelosuppression events in the 177Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm.

Three events suspected to be drug-related by the Investigator with fatal outcomes were reported, all in 177Lu-PSMA-617+BSC/BSoC arm: 2 deaths due to pancytopenia and 1 death due to bone marrow failure. The cases of pancytopenia and their clinical courses were complicated by progressive cancer and bone marrow involvement. The third patient was reported to have bone marrow failure on the same day as the first administration of ^{177}Lu-PSMA-617 and died 18 days later. On review he had profound anemia at screening and subsequently treatment-emergent thrombocytopenia was reported. At the time of patient's death, the events (fatigue, pain, dyspnoea, dry mouth, thrombocytopenia, anaemia, vomiting, weight decreased, and poor quality of sleep) were ongoing. It is not fully clear whether he suffered bone marrow failure as a result of ^{177}Lu-PSMA-617 treatment or bone marrow metastasis or other drugs had also impacted this outcome.

Lacrimal Toxicity: Radiation exposure of lacrimal glands it of particular interest, since dosimetry studies revealed this location as the region with the highest absorbed dose. In the pivotal Study PSMA-617-01 the number and severity of events reflecting lacrimal toxicity was rather low. Dry eye was only reported by 16 (3.0%) patients in the 177Lu-PSMA-617+BSC/BSoC arm, and 2 (1.0%) patients in the BSC/BSoC only arm. These were all grade 1 events and need no specific treatment, except for 1 related grade 2 event. Blurred vision as a potential complication of dry eyes events was reported by 9 (1.7%) patients in the 177Lu-PSMA-617+BSC/BSoC arm, and by 2 (1.0%) patients in the BSC/BSoC only arm. However, two (0.4%) of these patients in the 177Lu-PSMA-617+BSC/BSoC arm had high grade (≥3) with blurred vison events. Additional factors like pre-existing eye comorbidities or medication may be involved in these cases too.

Dry Mouth: Dry Mouth is a focused topic consisting almost entirely of reports of "Dry Mouth", but with 2 cases of Aptyalism. In the salivary glands, the mean radiation absorbed dose of ^{177}Lu-PSMA-617 was 0.63±0.36 Gy/GBq, which was on the lower side of the wide range of mean values (0.498 - 1.90 Gy/GBq) reported in the literature. Study PSMA-617-01 Safety-wise, treatment with ^{177}Lu-PSMA-617 has been associated with a frequent but relatively low severity of salivary gland toxicity (dry mouth/xerostomia) as reported in the literature (68% reversible grade 1/2 dry mouth reported by Hofman et al (2019). In accordance with this, and as anticipated from the mechanism of action and distribution to the salivary glands, this was a very frequently reported event in the 177Lu-PSMA-617+BSC/BSoC group (38.8% patients), but was infrequently reported in the BSC/BSoC only arm (0.5% patients). At data cut-off, more patients had unresolved events (26.1% patients) than resolved (13.2% patients) in the 177Lu-PSMA-617+BSC/BSoC arm.

Nausea and vomiting: As expected for a radiation-product for RLT, the frequency of nausea and vomiting was significantly higher than for BSC/BSoC alone. These types of AEs were approximately twice as high in the 177Lu-PSMA-617+BSC/BSoC arm (39.3% patients) as compared to the BSC/BSoC only arm (17.1% patients) as was expected. However, high grade events (≥3) were infrequent in either

arm (1.5% patients vs. 0.5% patients) and only 1 (0.2%) patient was withdrawn from ^{177}Lu-PSMA-617 treatment due to this category of events and in the BSC/BSoC.

Renal function: Renal Effects was selected as a safety topic of interest due to PSMA expression in the proximal tubule, and the known renal route of ^{177}Lu-PSMA-617 excretion. In the kidneys, the mean radiation absorbed dose was 0.43 ± 0.16 Gy/GBq, which is even lower than the lower end of the range of mean kidney radiation absorbed doses reported in the literature (0.49 - 0.991 Gy/GBq).

Renal events were more frequent in the 177Lu-PSMA-617+BSC/BSoC arm [46 (8.7%) versus 12 (5.9%) patients]. However, the incidence of high grade ≥3 events were similar between arms (3.4% patients vs. 2.9% patients) and there were no grade 4 or 5 renal events (i.e no events had a fatal outcome) in either arm; SAEs were even reported more frequently in the BSC/BSoC arm (3.4% patients) as compared to the 177Lu-PSMA-617+BSC/BSoC arm (1.7% patients). Nevertheless, the only event of renal failure was reported in the 177Lu-PSMA-617+BSC/BSoC arm and the rate of not recovered renal adverse events was higher in the 177Lu-PSMA-617+BSC/BSoC arm (3.4% versus 1.5%).

In general, a higher risk for renal impairment is likely to occur with RLT with ^{177}Lu-PSMA-617 in comparison with BSC/BSoC below a CCl of 54 mL/min.

Hepatotoxicity: Hepatic metastatic disease at baseline was balanced between the arms (11.0% versus 11.2%) and also hepatotoxicity events were reported with a similar incidence (≤5% differences) in both arms (10.2% patients vs. 7.8% patients). The high grade (≥3) events were of similar frequency (2.8% patients vs. 2.4% patients) in both arms, as were the SAEs (0.9% patients vs. 1.0% patients). No patient in either arm had a constellation of values indicative of Hy's law during randomized treatment. 2 fatal cases were not assessed as drug-related.

QT Prolongation: ^{177}Lu-PSMA-617 at the studied doses in the sub-study had no observed clinically relevant effects on QTcF. No event of "QT Prolongation" was reported in the PSMA-617-01 main study.The available hERG data indicate the absence for particular risks regarding QT prolongation from the product.

Second Primary Malignancies: Few patients had second primary malignancies events (13, 1.8% patients); the incidence was higher in the 177Lu-PSMA-617+BSC/BSoC arm as compared to the BSC/BSoC only arm (11, 2.1% patients vs. 2, 1.0% patients), however, the observation periods were significantly shorter in the BSC/BSoC only arm.

Reproductive Toxicity: This safety topic of interest was regarded as a potential risk due to the nature of this RLT treatment targeting a cancer of the genitourinary tract, even though the study population of mCRPC patients was considered not to have reproductive potential.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

In the pivotal PSMA-617-01 study, as could be expected in a BSC/BSoC only-comparative trial, **more patients in the 177Lu-PSMA-617+BSC/BSoC arm than in the BSC/BSoC only arm had SAEs** (**177-Lu-PSMA: 36.3%** vs **BSC/BSoC only: 27.8%**). The impact of radiation toxicity on safety becomes even more clearly in the frequency of **drug-related SAEs**, which occurred threefold in **9.3% patients in the 177Lu-PSMA-617**+BSC/BSoC arm and **2.4% patients in the BSC/BSoC only** arm.

The SOCs with TEAEs reported in at least ≥5% of the patients in either arm were (177-Lu-PSMA vs BSC/BSoC only) were infections and infestations (9.8% patients vs. 4.4% patients) followed by

nervous system disorders (6.8% patients vs. 7.8% patients) and blood and lymphatic system disorders (5.1% patients vs. 0.5% patients). Infections (Urosepsis, Pneumonia) and blood disorder (Cytopenia) are likely to be mostly drug related complications, while nervous system disorder SAEs may mainly reflect cerebral manifestation of the underlying disease.

Deaths

Overall, 85 patients died while on-treatment. More patients died patients in the 177Lu-PSMA-617+BSC/BSoC arm than in the BSC/BSoC only arm [66 patients (**^{177}Lu-PSMA-617: 12.5%** vs. **BSC/BSoC only**: 19 patients (**9.3%**)]. The **most frequent primary cause of death** during randomized treatment in both arms was **disease progression** (8.3% patients in the 177Lu-PSMA-617+BSC/BSoC arm vs. 6.8% patients in the BSC/BSoC only arm).

SAEs with fatal outcomes occurred only slightly more in the 177Lu-PSMA-617+BSC/BSoC arm: 19 **(3.6%)** patients in the **177Lu-PSMA-617+BSC/BSoC arm** (including 1 disease progression and 1 COVID-19); and **6 (2.9%)** patients in the **BSC/BSoC only arm** (including 1 disease progression). However, again the difference of treatment duration on randomized treatment between the arms need to be considered for interpretation, since it was significantly shorter in the BSC/BSoC only arm.

2.6.8.4. Laboratory findings

Hematology:

Table OS-5 Worst post-baseline hematological abnormalities based on CTC grades during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	177Lu-PSMA-617+BSC/BSoC N=529 n (%)		BSC/BSoC only N=205 n (%)	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Hemoglobin – Anemia	520 (98.3)	80 **(15.1)**	179 (87.3)	13 (6.3)
Lymphocytes – Decreased	480 (90.7)	269 **(50.9)**	141 (68.8)	39 (19.0)
Leukocytes – Decreased	307 (58.0)	36 **(6.8)**	54 (26.3)	4 (2.0)
Platelets – Decreased	258 (48.8)	49 (**9.3**)	49 (23.9)	5 (2.4)
Neutrophils – Decreased	149 (28.2)	23 (4.3)	20 (9.8)	2 (1.0)
Eosinophils – Eosinophilia	37 (7.0)	0	18 (8.8)	0
Hemoglobin – Increased	1 (0.2)	0	0	0
Lymphocyte – Increased	2 (0.4)	2 (0.4)	2 (1.0)	0

Source: [Study PSMA-617-01-Table 14.3.4.14.2]

The **most frequent myelosuppression-related adverse events were anaemia, thrombocytopenia, lymphocytopenia, leukopenia, and neutropenia**, which may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions, but which may also be impacted by bone marrow impairment at baseline from prior therapy. These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4. None of these hematological parameter shifts caused any unexpected safety concerns.

The following differences regarding hematology were noted between the 177Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm [inclusive of the high grade abnormalities (grade 3/4)]: low lymphocytes level (grade 3/4 abnormalities: 50.9% patients vs.

19.0% patients); anemia (grade 3/4 abnormalities: 15.1% patients vs. 6.3% patients); and low platelets (grade 3/4 abnormalities: 9.3% patients vs. 2.4% patients).

However, it is noted that, despite these expected hematology abnormalities, anemia, lymphocytopenia or thrombocytopenia that led to permanent discontinuation remained infrequent (<3.0% patients each); and these were observed with similar incidences in both treatment arms during randomized treatment.

In the BSC/BSoC only arm also a general trend of shifts towards higher grade abnormalities during randomized treatment was observed for low lymphocytes and low leukocytes, but to a lower extent and with relatively fewer shifts to higher grade abnormalities (grade 3 or 4) as compared to the 177Lu-PSMA-617+BSC/BSoC arm due to the absence of additional radiotoxicity. However, it needs to be considered that the current exposure probably not fully reflect the intended treatment duration of 6 cycles as recommended in the product information. It may be expected that particularly haematotoxicity will be more pronounced than obvious from the current data during longer treatment periods as foreseen in the SmPC.

The applicant reports that there was one case of AML observed during long term follow-up.

Clinical chemistry abnormalities observed during randomized treatment were generally similar in both treatment arms (≤10% differences) with few noteworthy exceptions of hyponatremia (38.2% patients vs. 24.9% patients); hypocalcemia (43.1% patients vs. 31.7% patients); and AST increased (31.2% patients vs. 21.0% patients). In both treatment arms, grade 3 / 4 abnormalities were infrequent (<3.0% patients). Some shifts to higher grades were observed during the randomized treatment period but there was no trend; and none of these shifts raised any safety concerns.

The liver function parameters were similar in both arms, and no notable high frequency was observed for any of the hepatic laboratory categories. The laboratory data did not raise any hepatic safety concerns. No patient in either arm had a constellation of values indicative of Hy's law during the randomized treatment. Also, during long term follow-up, liver function parameters were similar between both the groups of patients and similar to what was observed during the randomized treatment.

Analysis of serum testosterone failed to demonstrate clear trends or changes. Almost all patients had low testosterone level at baseline as per the inclusion criteria (<50 ng/dL or <1.7 nmol/L) and no shifts from low to normal testosterone levels were observed during randomized treatment.

2.6.8.5. Safety in special populations

The majority of the patient population in Study PSMA-617-01 was elderly (≥ 65 years), with only about one quarter of patients being below the age of 65 years at baseline. This is consistent with the median age at diagnosis of mCRPC being 70 years (Flaig et al 2016).

Table OS-6 Overview of TEAEs during randomized treatment by three age categories (<65; ⩾65-<75; ⩾75 years at baseline).

	177Lu-PSMA-617 +BSC/BSoC			**BSC/BSoC only**		
Type of TEAE	**<65 Years N=142**	**≥65-<75 Years N=244**	**≥75 Years N=143**	**<65 Years N=42**	**≥65-<75 Years N=100**	**≥75 Years N=63**
TEAE	136(95.8)	241 (98.8)	142 (99.3)	30 (71.4)	84 (84.0)	56 (88.9)
Serious TEAE	45 (31.7)	89 (36.5)	58 (40.6)	7 (16.7)	26 (26.0)	24 (38.1)

Table OS-6 Overview of TEAEs during randomized treatment by three age categories (<65; ⩾65-<75; ⩾75 years at baseline).						
	177Lu-PSMA-617 +BSC/BSoC			BSC/BSoC only		
Type of TEAE	**<65 Years N=142**	**≥65-<75 Years N=244**	**≥75 Years N=143**	**<65 Years N=42**	**≥65-<75 Years N=100**	**≥75 Years N=63**
Grade 3/4/5 TEAE	72 (50.7)	127 (52.0)	80 (55.9)	13 (31.0)	36 (36.0)	29 (46.0)
Drug-related TEAE	117 (82.4)	207 (84.8)	127 (88.8)	11 (26.2)	28 (28.0)	20 (31.7)
Serious drug-related TEAE	12 (8.5)	19 (7.8)	18 (12.6)	1 (2.4)	0	4 (6.3)
Drug-related grade 3/4/5 TEAE	37 (26.1)	65 (26.6)	48 (33.6)	2 (4.8)	1 (1.0)	5 (7.9)
TEAE leading to reduction of ^{177}Lu-PSMA-617	7 (4.9)	13 (5.3)	10 (7.0)	0	0	0
TEAE leading to reduction of BSC/BSoC	C 8 (5.6)	4 (1.6)	5 (3.5)	1 (2.4)	5 (5.0)	1 (1.6)
TEAE leading to interruption of ^{177}Lu-	21 (14.8)	40 (16.4)	24 (16.8)	0	0	2 (3.2)
PSMA-617						
TEAE leading to interruption of	10 (7.0)	23 (9.4)	17 (11.9)	1 (2.4)	5 (5.0)	8 (12.7)
BSC/BSoC						
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	14 (9.9)	27 (11.1)	22 (15.4)	0	0	1 (1.6)
TEAE leading to discontinuation of BSC/BSoC	12 (8.5)	21 (8.6)	12 (8.4)	3 (7.1)	11 (11.0)	2 (3.2)
Fatal TEAE	3 (2.1)	10 (4.1)	6 (4.2)	0	4 (4.0)	2 (3.2)

Source: [SCS Appendix 1-Table 35]

As shown in Table OS-6 above, the incidence of TEAEs (by most type and severity) were mostly slightly higher in the elderly subgroups of patients (≥65-<75 years age group and ≥75 years age group) in both arms, as compared to the <65 years age group. However, the differences were mostly ≤10%, with few exceptions.

Subgroup analyses present revealed a tendency towards higher incidences and severity in patients with ECOG score of 2 at baseline versus ECOG score 0 or 1, in patients ⩾65 years, patients with abnormal eGFR and proteinuria levels, renal impairment, and patients with concurrent radiation therapy in both the treatment arms; however, the shifts were more frequent in the 177Lu-PSMA-617+BSC/BSoC arm.

Within treatment arms, in both arms, the differences in incidence of TEAEs including TEAEs leading to discontinuation were ≤10% for White, and Black or African American patients with few exceptions. These differences were not notable and as the sample sizes were too low.

The proportion of White patients in each arms was highly predominant, while the number of Asian patients (<10 patients per arm) and Black or African American was relatively low. Hence, again these results should be interpreted with caution.

With respect to renal function at baseline, in both arms, the incidence of TEAEs by type and severity was slightly higher in the patients who had abnormal eGFR and positive proteinuria levels (impaired) versus not (non-impaired); however the differences were mostly ≤20% with few exceptions.

In the 177Lu-PSMA-617+BSC/BSoC arm, the differences between impaired versus non-impaired groups were greater for high grade TEAEs (77.4% patients vs. 50.5% patients), and serious TEAEs (67.7% patients vs. 32.9% patients). Similar difference (50.0% patients vs. 26.4% patients) was noted in the BSC/BSoC only arm for the serious TEAEs. In particular, the incidence of fatal TEAEs, though low in number overall, was 4 times more in the impaired group as compared with the non-impaired (12.9% patients vs. 3.0% patients) in the 177Lu-PSMA-617+BSC/BSoC arm and more than 2 times in the impaired group as compared with the non-impaired in the BSC/BSoC only treatment arm (7.1% patients vs. 2.7% patients).

With respect to the NAAD medication within each treatment arm, in both arms, the difference in incidences of TEAEs overall, by type and severity were generally ≤10%, in the presence or absence of NAAD during the randomized treatment; except for drug-related TEAEs in the BSC/BSoC only arm (37.4% patients vs. 10.6% patients).

Overall, no other clinically relevant trend or pattern was observed from the subgroup analyses presented. Considering the partially low numbers in the subgroups meaningful interpretation of changes observed seemed challenging and less reliable; chance findings may also be involved.

2.6.8.6. Immunological events

No information provided and probably not applicable for a RLT product.

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

^{177}Lu-PSMA-617 is metabolically stable both *in vitro* and *in vivo*, passively cleared through the kidneys and not a substrate of any of the investigated uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp and BCRP) based on *in vitro* assessments. Therefore, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions. Similarly, ^{177}Lu-PSMA-617 was not an inducer of CYP1A2, 2B6 and 3A4 and was also not an inhibitor of all common CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5), and investigated efflux and uptake transporters. Therefore, 177Lu-PSMA-617 will not be the cause of any CYP- or transporter-mediated drug interactions. The safety and efficacy of ^{177}Lu-PSMA-617 have not been established in females as ^{177}Lu-PSMA-617 is not indicated for use in females; therefore, there are no available data on the use of ^{177}Lu-PSMA-617 in pregnant or lactating women.

2.6.8.8. Discontinuation due to adverse events

Treatment discontinuation due to TEAEs was relatively rare and balanced in the pivotal trial PSMA-617-01. Permanent discontinuation of BSC/BSoC due to TEAEs was only slightly less frequent than in the 177Lu-PSMA-617+BSC/BSoC treatment arm (45, **8.5% patients** in the 177Lu-PSMA-617+BSC/BSoC arm vs. 16, **7.8% patients** in the BSC/BSoC only arm). The **most frequent TEAEs leading to discontinuation of 177Lu-PSMA-617 were myelosuppression related events (5.1%)**. 2.8% patients each with thrombocytopenia and anemia; 1.3% patients with leukopenia; 0.8% patients with neutropenia, and 0.6% patients with pancytopenia) probably reflecting the impact of radiation, while symptoms associated with disease progression (particularly spinal cord compression) were the main cause for TEAE related discontinuation in the BSC/BSoC only arm.

2.6.8.9. Post marketing experience

Lutetium (177Lu) vipivotide tetraxetan containing ^{177}Lu-PSMA-617 **has not received marketing authorization in any country**. **No commercially available 177Lu-PSMA product is currently approved in the EU.**

2.6.9. Discussion on clinical safety

The main safety evaluation was based on safety data from a single pivotal study, PSMA-617-01 which is a phase III, open-label, randomized study in patients with progressive PSMA-positive mCRPC. Supportive safety data are derived from the phase 2 study PSMA-617-02 using a different dose regimen (6.0 GBq or 7.4 GBq, every 8 weeks for 4 cycles). Also, ECG data from a single arm sub-study (N=30) which recruited the same patients as the pivotal study was provided. The safety reporting was done in patients in the FAS who received at least 1 dose of randomized therapy (FAS safety analysis set). Considering the replication of results by the supportive study, safety data derived from a single pivotal study is considered acceptable. However, it cannot be excluded that the open-label design of the pivotal study may have affected safety reporting.

Pooling of safety data across these studies was not possible, since both trials differ regarding the study design, the treatment regimen used and the approach for safety data collection. Mainly the fact that AESI categories had not been defined while these data were analyzed and only SAEs were graded using CTCAE, limit the supportive value of data from Study PSMA-617-02. Moreover, trial PSMA-617-02 was small and early terminated due to acquisition of PSMA-617 by a different company, who initiated the pivotal trial PSMA-617-01. Thus, the main relevant source for safety assessment in this application remains trial PSMA-617-01. However, data from trial PSMA-617-02 may allow to some degree assessing dose-depending toxicities of ^{177}Lu-PSMA-617.

It is important to note that the safety profile derived from this study is not from ^{177}Lu-PSMA-617 given as monotherapy, because concomitant anti-cancer medications were allowed during the study, such as GNRH agonists/antagonists, anti-androgens and novel androgen axis drugs. The latter are considered to be more relevant for the observed safety profile and were received by 52.6% of the patients in the ^{177}Lu-PSMA-617 arm and 67.8% of the patients in the BSC arm. The use of these medications in this setting is considered acceptable, since this is reflective of clinical practice, and reflected in the finally agreed indication (see also clinical efficacy section). The imbalance in anti-androgens may have slightly favoured the safety profile for the ^{177}Lu-PSMA-617 arm compared with the control arm.

Safety assessments consisted of AEs, laboratory data, and vital signs, which is deemed sufficient for evaluation in this application. Moreover, in general the provided documents are adequately structured and informative to allow a valid assessment.

Non-clinical data revealed the almost complete absence of intrinsic toxicity of non-radioactive (unlabelled) PSMA-617. This means that adverse events and safety profile of the applied product is dominated from radiation effects in target cells as well as off-target organs.

Dosimetry demonstrated that cell salivary glands, renal tubular cells, and small intestine tissues express PSMA; however, expression is restricted and several hundred-fold lower. Nevertheless, symptoms of toxicities in these organs are likely to be drug-related and are defined as adverse events of special interest (AESI).

As per data from dosimetry studies, the largest radiation absorbed dose is in the lacrimal glands. However, only low frequency and low-grade AEs of dry eye are reported in the literature. In the other

side, it remains uncertain whether this issue was sufficiently evaluated in other published trials. With respect to the cumulative radiation-dose, literature data suggest that a ^{177}Lu-PSMA-617 total cumulative dose 50 GBq could be administered without long-term salivary gland toxicity (Virgolini et al 2018).

The kidney, as the primary route of ^{177}Lu-PSMA-617 excretion and a PSMA-expressing tissue, is exposed to ^{177}Lu-PSMA-617; however, nephrotoxicity has not been notable in any safety series before. In the Hofman prospective Phase II LuPSMA study, grade 1-2 renal injury are reported in 10% of patients and a mean decline of 51Cr-EDTA eGFR of 11.7 mL/min (95% CI -19 to -4 mL/min) was observed in 28 patients who had 51Cr-EDTA eGFR measured before and 3 months after completion of ^{177}Lu-PSMA-617 (Violet et al 2020). Scarpa et al (2017) noted these results and reasoned that a biologically effective dose for ^{177}Lu-PSMA-617 could be as high as 61.66+/-35.97 GBq. However, though available published literature data do not show renal toxicity to be an important safety concern during treatment with ^{177}Lu-PSMA-617, it needs to be considered that due to the possibility of radiotoxic damage to this exposed tissue, renal toxicity may still present a risk in months to years following treatment also for ^{177}-Lu-PSMA. In particular, if a high dose regime was administered like in the pivotal trial. However, considering the overall low life expectance of an advanced mPC population, the importance of renal toxicity may be probably rather limited. According to the trials inclusion/exclusion criteria it was agreed that Pluvicto should not be used in patients with moderate renal impairment, specifically within the range of CLcr 30 to < 50 mL/min as well as in patients with severe renal impairment (CLcr < 30 mL/min), while treatment in patients with moderate renal impairment within the range of CLcr ≥ 50 to 59 mL/min is acceptable(see SmPC section 4.2). Use in "patients with severe renal impairment" is included as missing information in the RMP (see section 2.7.1).

More clarification regarding the impact of renal impairment can be expected from the planned trial Study CAAA617A12202, which was a requirement for approval by FDA.

Although in the non-diseased bone marrow a lack of PSMA expression was demonstrated and published dosimetry studies with ^{177}Lu-PSMA-617 highlight that the average bone marrow absorbed radiation doses are low, it needs to be considered that higher burden of metastatic disease in the bone marrow may increase radiation exposure in the bone marrow. Moreover, prior therapies in the applied mCRPC population with cytotoxic drugs and PSMA negative PC bone-marrow infiltration may reduce the normal capacity of bone marrow function in addition. Literature data report that radiation absorbed dose limits have been defined for EBRT induced haematological damage at 2 Gy, while radiobiological estimation calculate a tolerable ^{177}Lu-PSMA-617 cumulative dose for bone marrow of 45 to 73 GBq (Kabasakal et al 2017, Scarpa et al 2017).

Summarising the known safety observations as documented in the publish literature following ^{177}Lu-PSMA-617 treatment the drug's known toxicities to date appear to be predominantly grade 1/2, reversible, and most frequently seen as salivary gland, haematological and gastrointestinal toxicity. The incidence of grade 3/4 toxicities is low, and mainly restricted to reversible haematological events. Frequent hematologic toxicities or myelosuppression related events noted are anaemia, thrombocytopenia, lymphocytopenia and neutropenia, which may be due to significant bone marrow impairment at baseline. Well described off-target toxicities are dry mouth, which is reported as reversible grade 1/2, with no reports of >grade 2 dry mouth in the literature, while reversible grade 1/2 dry eyes have been reported much less frequently. Interestingly, nephrotoxicity was not been notable in any of the published safety series. The most frequent non-haematological toxicities associated with ^{177}Lu-PSMA-617 treatment are reported to be nausea, vomiting, dry mouth, decreased

appetite, pain and fatigue. These are seen as non-specific, but are likely to be attributed to the administration of therapeutic levels of a radioactive compound.

With respect this application, it is important to understand that the current posology, which recommends treatment regimen for ^{177}Lu-PSMA-617 for a total of 6 cycles (doses) of 7.4 GBq administered intravenously every 6 weeks (± 1 week) is a significant dose escalation compared with the previous experience, including a high dose, more intensive treatment with shorter recovery periods and more cycles than previous experience. Although it is acknowledged that the trial was successful, data revealed that the radiation-related off-target toxicity was obviously significantly higher than in other trials. Although it is acknowledged that the significant difference in treatment duration between the two arms may have contributed also and biased the outcome significantly in favour for subjects BSC/BSoC, the uncertainty that there may be a potential for ameliorated tolerability at a lower dose level remains.

Exposure

Overall, N=593 patients were exposed to ^{177}Lu-PSMA-617, N=529 patients in the pivotal study and N=64 in supportive study. The median follow up for the safety analysis set was 14.13 months (range: 0.6-31.5). Around N=88 patients (16.6%) received treatment for at least 1 year in the experimental arm. A small number of patients received treatment longer than 1 year. While these samples are small, this is considered sufficient to establish the safety profile.

The longer median duration of exposure in the ^{177}Lu-PSMA-617 arm (7.8 months) compared with the control arm (2.1 months) could be reflective of better efficacy considering that most patients discontinued treatment due to disease progression (23.0% versus 26.1%). In the ^{177}Lu-PSMA-617 arm 46.5% of the patients had received 6 cycles of ^{177}Lu-PSMA-617 and 67.7% patients received at least 4 cycles. The decision whether full 6 cycles should be given in the trial depended on the investigators decision based an individual benefit-risk assessment and is acceptable since it may reflect the clinical practise.

Cycles were mostly delayed due to scheduling purposes (10.6%) and in 7.6% of the patients due to AEs. One dose reduction (by 20%) in administered activity was permitted and these were observed in 5.7% of the patients, all due to AEs. These numbers could not be compared with the BSC arm due to the open label nature of the study.

The SmPC recommended dose for ^{177}Lu-PSMA-617 is 7 400 MBq (200 mCi) every 6 weeks (±1 week) for a total of 6 doses. This corresponds to an overall treatment duration of 9 months and a total radiation dose of about 44.400 MBq.

The median and mean of duration of exposure is about 6.3 or 7.9 months only. Moreover, the details regarding the number of cycles in the 177Lu-PSMA-617+BSC/BSoC arm of the pivotal trial PSMA-617-01 reveal that only 46.5% of the patients received the full recommended treatment of 6 cycles of ^{177}Lu-PSMA-617, while 67.7% received at least 4 cycles, the minimum recommended per protocol. This means that more than the half of the FAS Safety population was not exposed to the intended full treatment course of 6 cycles and the full dose of ^{177}Lu-PSMA-617 due to the investigator's decision. However, as the rate of adverse events reported in the different cycles is balanced, this may be acceptable.

In summary, it may be presumed that the safety profile characterised by the exposed population does not fully reflect the treatment risks and may lead to an underestimation of the toxicity in the case all subjects would have been exposed with 6 cycles of treatment.

On the other side, it needs to be considered that since the majority of the patients in the BSC/BSoC only arm (97.6%) patients discontinued treatment early, exposure in the comparator arm was significantly lower [Mean 3.5 (3.9), Median 2.1 months], which clearly has biased the safety outcome in the BCS/BSoC only arm favourable. Considering the totality of data the proposed posology seems acceptable.

Otherwise, it is agreed that the demographic and baseline disease characteristics were well balanced between the 2 treatment arms, and were representative of the mCRPC patients with an advanced disease.

Adverse events

As could be expected in a comparison to BSC/BSoC more pronounce safety risks were observed during ^{177}Lu-PSMA-617. Overall, all relevant key safety characteristics (TEAEs, drug-related TEAEs, grade ≥3 events, as well as SAEs including fatal SAEs) were usually more frequent in the 177Lu-PSMA-617+BSC/BSoC arm.

The higher rates of TEAEs and SAEs in general (PSMA:36.3% vs BSC: 27.8%) are may be caused by the disease, as illustrated by the significantly lower rates of drug-related SAES (PSMA: 9.3% vs BSC: 2.9%). Considering the similar rates of investigator-assessed SAEs with a fatal outcome (PSMA:3.6% vs BSC:2.9%) higher incidences may also reflect the significantly shorter treatment duration in the BSC/BSoC arm . This means that the period for reporting adverse events was more than twofold longer in the 177Lu-PSMA-617 arm and thereby may have (partially) contributed significantly to the observed differences in TEAEs and SAEs.

In the PSMA-617-01 study, the incidence of TEAEs by SOC (for all SOCs) was higher in the 177Lu-PSMA-617+BSC/BSoC arm.

The greatest differences (≥20%) between the 2 treatment arms (177Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were observed for gastrointestinal disorders (PSMA: 75.4% vs BSC: 31.7% of patients), general disorders and administration site conditions (PSMA: 61.2% vs BSC: 38.5% of patients) and blood and lymphatic system disorders (PSMA: 47.8% vs BSC: 18.0% of patients).

Although grade ≥3 TEAEs in general were relatively infrequent (<5.0% in either arms), some differences are noted, in particular with respect to myelosuppression events as anaemia, thrombocytopenia, and lymphocytopenia), which were more frequent in the 177Lu-PSMA-617+BSC/BSoC arm. It is noted that these events were more frequent (in the range of 6-13% frequency), but only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤3.0% of the patients.

TEAEs with the greatest differences (≥10%) in the incidence between the 2 treatment arms (177Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were observed regarding fatigue (PSMA: 43.1% vs. BSC:22.9%), anemia (PSMA: 31.8% vs. BSC 13.2%), thrombocytopenia (PSMA: 17.2% vs. BSC:4.4%) as well as lymphopenia (PSMA: 14.2% vs BSC: 3.9%) and leukopenia (PSMA:12.5% vs. BSC: 2.0%). Moreover, probably in the context of the decrease leucocytes urinary tract infection were also more frequent (PSMA: 11.0% vs BCS: 1.0% patients).

Interestingly, spinal cord compression as a SSE was observed with a lower frequency in the 177Lu-PSMA-617+BSC/BSoC arm (1.3% patients vs. 5.4% patients in the BSC/BSoC arm), which may be seen as a treatment associated benefit in principle. However, the small number of events and the difference in observational period does not allow a valid interpretation and may represent also a chance finding.

Hepatotoxicity events were also reported to be slightly with higher with a higher incidence (less than 5% differences) in both arms (10.2% patients vs. 7.8% patients); and again only very few events led to withdrawal of ^{177}Lu-PSMA-617 (0.6% patients).

Second Primary Malignancies as consequence of the radiation were infrequent events in both arms (2.1% patients vs. 1.0% patient). The events were skin cancers and metastases to the brain or meninges. When excluding metastatic events the following events were reported in the ^{177}Lu-PSMA-617+BSC/BSoC treatment arm: squamous cell carcinoma (4 patients), basal cell carcinoma, malignant melanoma, squamous cell carcinoma of the skin (1 patient each). However, one case of acute myeloid leukemia (AML) was reported outside of the treatment-emergent period, after the 30-day post-treatment follow-up, but before capture of long-term follow-up events. As in other RLTs before, the important risk for haematological malignancies like leukemia and MDS is not fully evaluable from the data submitted, but it is possible to estimate this risk from the type of radiation from other RLTs and the cumulative dose administered. Second Primary Malignancies are therefore considered to be class effect. Data on this second primary malignancies were reported in section 4.8 under the header of "Description of selected adverse reactions" as a class effect. Also since the incidence of second primary malignancies is considered relevant information for prescribers and patients. Second Primary Malignancies were included as important potential risk in the RMP. As in other RLT, mature data regarding this issue can be expected only from a longer follow up.

In the PSMA-617-01 study, long-term follow-up safety data was collected after the end-of-study visit for a duration of 24 months or until 508 deaths (whichever occurred first). According the applicant's reports the incidences of AEs by SOC were similar (≤10% differences) for those patients who had previously received 177Lu-PSMA-617+BSC/BSoC. All other events selected as potential safety topic of interests (QT Prolongation, Intracranial Hemorrhage, Reproductive Toxicity) were reported for <2.0% of patients in both arms, and withdrawal of ^{177}Lu-PSMA-617 was attributed to such events in either 0 or 1 patient (0.2%) in the 177Lu-PSMA-617+BSC/BSoC arm.

In general, it is reassuming that no new or additional signals were identified and no obviously dramatic increase in toxicities was observed with the high dose posology on the first glance.

The criteria for the first screening and identification of adverse drug reaction (ADR) candidates for reporting in the labelling was any AE (MedDRA PT) which occurred in ≥5% of patients treated with ^{177}Lu-PSMA-617 arm or with a difference of ≥2% compared with the BSC/BSoC control arm. AEs with reported frequencies of <5%, or additional AEs observed in other supporting studies and the literature, or additional data were also considered as ADR candidates based on clinical assessment of specificity, severity and plausibility. ADR candidates then underwent medical review to ascertain whether or not each should be considered as an ADR related to ^{177}Lu-PSMA-617.

SAEs

Overall SAEs were reported more frequently in the ^{177}Lu-PSMA-617 arm (36.3%) compared with the BSC arm (27.8%), however frequencies of individual SAEs were generally low (<2%) except for anaemia (2.8% vs 0.5%), urinary tract infection (2.5 vs 0.5%), haematuria (2.1% vs 0.5%) and spinal cord compression (1.1% vs 4.9%). As stated before, this is indicative of more severe toxicity of 177Lu-PSMA-617 plus BSC compared with BSC alone, apart from the difference in spinal cord compression that could be efficacy-related.

Deaths

Overall, 85 patients died while on treatment: 66 (12.5%) patients in the 177Lu PSMA 617 arm, and 19 (9.3%) patients in the BSC arm. The most frequent cause of death was disease progression in both

arms (respectively 8.3% vs. 6.8%). Further, three (0.6%) patients died of unknown causes in the 177Lu PSMA 617 arm, while there were no unknown death causes in the BSC arm. Deaths due to TEAEs (not including the deaths due to disease progression erroneously collected in this category prior to a protocol amendment which corrected this) were observed in 18 (3.4%) patients in the 177Lu-PSMA-617 arm (including 1 case of COVID 19); and 4 (2.0%) patients in the BSC arm. Three on-treatment deaths were reported by the investigator to be related to 177Lu-PSMA-617 treatment (versus none in the control arm): two patients died due to pancytopenia, and 1 death due to bone marrow failure, all three a consequence of the myelosuppression caused by177Lu-PSMA-617 treatment. In addition, it is noted that in the 177Lu-PSMA-617 arm, but not in the control arm, there are several deaths not considered related to treatment. However, the deaths by intracranial haemorrhage were considered possibly or definitively related by the investigator, it is supported that Intracranial haemorrhage, is proposed by the Applicant as an important potential risk in the RMP. In addition, routine pharmacovigilance activities beyond ADRs reporting and signal detection included specific adverse event follow-up checklists, which will be used to collect further data to help characterize and/or closely monitor the respective risk.

Laboratory findings

Beside the haematological TEAE discussed above, clinical chemistry abnormalities observed during randomized treatment were generally similar in both treatment arms (≤10% differences) with few noteworthy exceptions of hyponatremia (38.2% patients vs. 24.9% patients); hypocalcemia (43.1% patients vs. 31.7% patients); and AST increased (31.2% patients vs. 21.0% patients). In both treatment arms, grade 3 / 4 abnormalities were infrequent (<3.0% patients).

The impact of the underlying disease itself as well as the cytotoxic pre-treatment seems to be reflected also by the observation that many patients had already low grade hematology abnormalities (grade 1 or 2) at baseline in both the treatment arms and for all hematology parameters analyzed. However, such observations are not unusual in cancer trials at baseline.

The liver function parameters were similar in both arms, and no notable high frequency was observed for any of the hepatic laboratory categories. The laboratory data did not raise any hepatic safety concerns. No patient in either arm had a constellation of values indicative of Hy's law during the randomized treatment. Also during long term follow-up, liver function parameters were similar between both the groups of patients and similar to what was observed during the randomized treatment.

Vital signs

The non-clinical data do not appear to indicate an effect of 177Lu PSMA-617 on the cardiac electrophysiology, however no dedicated clinical QT/QTc study was performed and ECGs were not automatically collected during the PSMA-617-01 study, only one ECG at screening was performed. The Applicant, however, did perform a single arm sub study in 30 patients at sites in Germany. This is considered to be a suboptimal situation as a QT/QTc study should ideally be performed prior to the phase 3 study as systematic monitoring might be needed in the phase 3 trial.

Safety topics of interest

The Applicant defined safety topics of interest which included AESIs for 177Lu-PSMA-617 as well as other safety topics considered standard for a comprehensive safety review. Most of these events occurred more frequent in the 177Lu-PSMA-617 arm compared with the control arm. The following events were defined to be of interest; fatigue (49.1% vs. 29.3%), myelosuppression (47.4% vs.

17.6%), dry mouth (39.3% vs. 1.0%), nausea and vomiting (39.3% vs 17.1%), hepatotoxicity (10.2% vs 7.8%), renal effects (8.7% vs 5.9%) and second primary malignancies (N=11 [2.1%] vs N=2 [1.0%]) . Intracranial haemorrhage (1.3% vs 1.5%) and reproductive toxicity (0.2% vs 0%) were observed at more or less comparable rates compared with the control arm. Grade ≤3 AEs were not observed frequently with the exception of myelosuppression events (23.4% vs 6.8%) and fatigue (7.0% vs 2.4%). Most of the safety events were treatment related, but did not lead to large tolerability issues (i.e. discontinuations and dose reductions/interruptions), except for myelosuppression events. It is not known whether the treatment-emergent AEs related to the safety topics of interest resolved over time as these data were not collected by the Applicant. Collection and submissioin of data on risks of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications, and potential of secondary malignancies. have been recommended (PAM-REC).

According to dosimetry data collected in the single arm sub-study the lacrimal glands (92 mGy), salivary glands (28 mGy), left colon (26 mGy), rectum (25 mGy), kidneys (19 mGy), right colon (14 mGy), urinary bladder (14 mGy) and thyroid (11 mGy) absorb the highest doses.

Myelosuppression events led to (at least one event of) dose interruption in roughly 20%, dose reduction in 8% and discontinuation in 15% of the patients, while tolerability issues were barely seen in the control arm. As previously stated there were 3 treatment related deaths due to myelosuppression events. Myelosuppression events are reported in section 4.4 and section 4.8 of the SmPC, and treatment recommendations in section 4.2, which is considered acceptable. Myelosuppression is considered important identified risk (RMP).

From the 39.3% (vs. 1.0%) of patients with dry mouth in the 177Lu-PSMA-617 arm, there were no Grade ≥3 TEAEs of dry mouth observed.

High grade (≥ 3) nausea and vomiting events were infrequent in both arms (1.5% vs. 0.5%). In the protocol, prophylactic therapy and antiemetic treatment were recommended at the discretion of the investigator. Considering that all these options are well established as clinical standards no additional recommendation regarding this issues are needed in the product information in the Rapporteur's view.

No events of QT prolongation were observed, however ECGs were not made systematically and no dedicated QT/QTc study was performed. Thus, it remains uncertain whether 177Lu-PSMA-617 does not influence the QT interval. Although no preclinical safety concerns were raised with regard to QT prolongation, the clinical data do not provide sufficient reassurance that 177Lu-PSMA-617 does not influence the QT interval; in the PK-ECG sub-study the concentration-QTc model predicts mean QTcF increase with an upper CI >10ms at Tmax, there were more events related to QT prolongation in the 177Lu-PSMA-617 compared to the BSC arm and there was no systematic ECG monitoring during the pivotal study. The Applicant was recommended to perform a QTc (sub)study as part of post authorisation Study CAAA617A12202, and provide the results of this (sub)study in order to conclude whether 177Lu-PSMA-617 leads to QTc effects.

From the data provided by the Applicant, ocular events do not appear to occur more frequently in patients with an AE of dry eye in the ^{177}Lu-PSMA-617+BSC/BSoC treatment arm. It can be considered acceptable that the occurrence of dry eye is used as a proxy for lacrimal toxicity here. However, it is noted that ocular events are observed more frequently in patients who received a cumulative dose over 14.8 GBq compared to below and equal to 14.8 GBq. This is also in accordance with published literature data were the frequency of dry exe TEAEs was about ~10% lower than in the pivotal trial Though the effect of time on treatment (and thus time to develop an AE) may have also influenced these outcomes. Overall, it can be agreed that no labeling changes are proposed related to the eye disorders SOC in Table 2 of the EU SmPC within section 4.8.

Safety in special populations

Many subgroup analyses for safety were performed. Subgroup analyses in the LuPSMA617+BSC arm by age (<65 [N=142]; ≥65-<75 [N=244]; ≥75 [N=143] years at baseline) indicate no large differences in safety between the different age categories in the experimental arm.

As typical for the mCRPC population, the majority of the patient population in Study PSMA-617-01 was elderly (≥ 65 years), with only about one quarter of patients being below the age of 65 years at baseline. This is consistent with the median age at diagnosis of mCRPC being 70 years (Flaig et al 2016).

There was a trend of more TEAEs and more severe TEAEs with increasing patient age in both the 177Lu-PSMA-617+BSC/BSoC arm and in the BSC/BSoC only arm; however, this trend was not of specific concern in the eldest category of patients (≥75 years) and differences were mostly ≤10%, with few exceptions. In general, treatment with ^{177}Lu-PSMA-617 did not appear to a significant increase regarding the differences in the incidence of TEAEs between the age groups when compared with the differences in the incidence of TEAEs between the age groups seen in the BSC/BSoC only arm. This is reassuring considering the different medians of treatment durations in the both arms.

Moreover, a tendency towards higher incidences and severity was observed in patients with ECOG score of 2 at baseline versus ECOG score 0 or 1, in patients ≥65 years, patients with abnormal eGFR and proteinuria levels, renal impairment, and patients with concurrent radiation therapy in both the treatment arms.

Patients with a creatinine clearance <50 mL/min were not allowed to be included in the study. There is few information on patients with renal and hepatic impairment. The Applicant compared patients with baseline renal impairment via medical history (yes/no). There were few patients with renal impairment in the medical history (N=11 in the ^{177}Lu-PSMA-617 arm vs N=2 in the control arm). In the ^{177}Lu-PSMA-617 arm, patients with renal impairment had a less favourable safety profile compared to patients without renal impairment in their history, exemplified by higher frequencies of severe AEs (81.8% vs 52.1%), SAEs (63.6% vs 35.7%) and discontinuations (18.2% vs 11.8%). The number of patients in the control arm with renal impairment was too small for comparison. (Refer to the discussion on clinical pharmacokinetics for labelling consequences for patients with renal impairment.)

Patients with ALT or AST >3.0 ×ULN or >5.0 × ULN for patients with liver metastases were not allowed to be included in the pivotal study. There were no patients with hepatic impairment at baseline and thus there were no safety analyses for patients with hepatic impairment. (Refer to the discussion on clinical pharmacokinetics for labelling consequences for patients with hepatic impairment.)

Overall, no other clinically relevant trend or pattern was observed from the subgroup analyses presented. Considering the partially low numbers in the subgroups meaningful interpretation of changes observed seemed challenging and less reliable; chance findings may be also be involved.

Safety related to drug-drug interactions

No clinical drug-drug interaction studies were performed by the Applicant. ^{177}Lu-PSMA-617 is metabolically stable both *in vitro* and *in vivo*, passively cleared through the kidneys and not a substrate of any of the investigated uptake or efflux transporters (i.e. MATE1, MATE2-K, OAT1, OAT3, OCT2, P-gp and BCRP) based on *in vitro* assessments. Therefore, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions.

Similarly, ^{177}Lu-PSMA-617 was not an inducer of CYP1A2, 2B6 and 3A4 and was also not an inhibitor of all common CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5), and investigated efflux and uptake transporters. Therefore, ^{177}Lu-PSMA-617 will not be the cause of any CYP- or transporter-mediated drug interactions. It is concluded that drug-drug interactions due to ^{177}Lu-PSMA-617 are not a concern. No other additional interactions have to be discussed.

Discontinuation due to safety events

Discontinuation due to TEAEs was higher in the ^{177}Lu-PSMA-617 treatment compared with BSC/BSoC, but in total low. The most frequent TEAEs leading to ^{177}Lu-PSMA-617 discontinuation were mylosuppression related events (2.8% patients each with thrombocytopenia and anemia; 1.3% patients with leukopenia; 0.8% patients with neutropenia, and 0.6% patients with pancytopenia). All other TEAEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 were reported in ≤0.5% of patients each.

The most frequent TEAEs leading to permanent discontinuation of BSC/BSoC in the 177Lu-PSMA-617+BSC/BSoC arm were anemia, fatigue, thrombocytopenia (0.9% patients each), which were all also observed in the 177Lu-PSMA-617+BSC/BSoC arm.

The safety risks due to treatment with 177Lu-PSMA-617+BSC/BSoC arm were not identified as an important risk for treatment discontinuation.

No additional safety signal was derived from the supportive data from Study PSMA-617-02 and no further discussion of this data is deemed meaningful.

Supportive study

In the supportive study PSMA-617-02, similar types of AEs were observed as reported for the pivotal study, albeit that frequencies of severe (14.1%) and serious (18.8%) TEAEs and TEAEs leading to dose reduction (3.1%) and discontinuation (1.6%) were much lower. There was only one patient with a severe AE related to myelosuppression (one case of thrombocytopenia [1.6%]). This may be due to a different dosing schedule (6.0 GBq or 7.4 GBq, every 8 weeks for 4 doses in the supportive study versus 7.4 GBq every 6 weeks for 6 doses in the pivotal study). This questions whether there may be a potential for ameliorated tolerability at a lower dose level. The tolerability and severity of AEs may thus be improved with a lower dose however, it is unknown this would maintain similar clinical benefit.

Remaining safety topics

Considering the nature of the product it is acceptable that ADA's were not analysed. No cases of overdose with ^{177}Lu PSMA-617 have been reported in the 2 prospective clinical studies PSMA-617-01 and PSMA-617-02. The Applicant considers that the possibility of an overdose of ^{177}Lu PSMA-617 is unlikely, as a single dose vial with the predefined amount of radioactivity (7.4 GBq [±0.10]) is used and is administered by specific healthcare providers. This can be agreed.

Inadvertent radiation exposure has been included as important potential risk in the RMP. Educational materials for patients and their relatives were deemed necessary to address this risk (see RMP).

2.6.10. Conclusions on the clinical safety

Adding ^{177}Lu-PSMA-617 to BSC leads to a more unfavourable safety profile compared with BSC alone. This is exemplified by the higher numbers of all-causality and treatment-related AEs, severe AEs, SAEs, and treatment-related deaths. The largest differences in AEs between the two treatment arms are observed in the SOCs Gastrointestinal disorders (AEs: dry mouth, nausea, diarrhoea, vomiting,

constipation), General disorders (AE: fatigue) and Blood and lymphatic system disorders (AEs: anaemia, thrombocytopenia, lymphopenia and leukopenia). Noteworthy are the AEs of myelosuppression which are mostly treatment-related and the main causes of severe AEs, SAEs, treatment-related deaths, and tolerability issues.

A bias to the disadvantage of ^{177}-Lu-PSMA-617 may be a potential reason for the imbalances in exposure, due to a significantly shorter exposure in the BSC/BSoC arm. More than the half of the FAS Safety population included in this assessment was not exposed to the planned treatment course of 6 cycles and the intended full dose of ^{177}Lu-PSMA-617 due to the investigator's decision. Thus, the safety profile presented may not fully reflect the treatment risks of the applied posology. An underestimation of the toxicity may even be presumed also, since frequency and particularly severity of AESI are likely to depend from the total dose administered and may increase during longer treatment.

Overall, although the safety aspects were sufficiently covered, the safety profile of ^{177}Lu-PSMA-617 is considered non-negligible and should be weighed against the efficacy. For each patient, the radiation exposure must be justifiable by the likely benefit (see SmPC 4.4).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 21: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Myelosuppression • Renal toxicity
Important potential risks	• Intracranial hemorrhage • Inadvertent radiation exposure • Second primary malignancies
Missing information	• Patients with severe renal impairment

2.7.2. Pharmacovigilance plan

Table 22: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PSMA-617-01 (VISION): An international, prospective, open-label, multicentre, randomized phase 3 study of lutetium (^{177}Lu) vipivotide tetraxetan in the treatment of patients with progressive PSMA positive metastatic castration-resistant prostate cancer (mCRPC)	The extended 12-month long-term follow-up period will include the collection of survival and new treatment information, adverse events assessment for renal toxicity and secondary malignancies, and results of haematology and chemistry testing.	Renal toxicity Second primary malignancies	Final CSR	31-Mar-2025

2.7.3. Risk minimisation measures

Table 23: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Myelosuppression	**Routine risk minimization measures**: Section 4.2, 4,4, 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Renal toxicity	**Routine risk minimization measures:** Section 4.2, 4.4, 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** PSMA-617-01 (VISION)
Intracranial hemorrhage	**Routine risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		signal detection: Targeted follow-up checklist **Additional pharmacovigilance activities:** None
Inadvertent radiation exposure	**Routine risk minimization measures:** Section 4.2, 4.4, 4.9, 6.6 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Patients Guide
Second primary malignancies	**Routine risk minimization measures:** Section 4.8 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** PSMA-617-01 (VISION)
Patients with severe renal impairment	**Routine risk minimization measures:** Section 4.2, 5.2 of SmPC	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 23.03.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Pluvicto (lutetium (^{177}Lu) vipivotide tetraxetan) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Pluvicto 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).

3.1.2. Available therapies and unmet medical need

Current clinical guidelines (2021 EAU; and 2020 ESMO guidelines on prostate cancer) recommend the following (approved) medicinal products for the treatment of mCRPC, basing the choice of treatment on the patient's performance status, symptoms, co-morbidities, location and extent of disease, genomic profile, preference, and on the previously received treatment(s) in the (still) hormone-sensitive disease setting (in alphabetical order): abiraterone, cabazitaxel, docetaxel, enzalutamide, olaparib, 223Ra-dichloride).

Regarding the **unmet medical need**, on the one hand it is noted that approved treatments exist for (at least) part of the target population. On the other hand, few therapeutic options exist for patients with mCRPC who have previously received a NAAD as well as taxane-based chemotherapy (i.e. either docetaxel, or both docetaxel and cabazitaxel), and there thus remains an unmet medical need for (effective) new treatment options.

^{177}Lu-PSMA-617 has been used experimentally in the clinic since 2013 for the treatment of patients with mCRPC (Ahmadzadehfar et al 2015). As a result, published data on efficacy (and safety) of ^{177}Lu-PSMA-617 in patients with mCRPC is available from many centers. Moreover, PSMA ligand, can be also

radiolabeled with gallium-68 (^{68}Ga) and used to identify PSMA expression and determine the local extent of disease by PET imaging. Therefore, ^{68}Ga-PSMA-11 PET/CT imaging is used as a component of eligibility criteria.

While the efficacy results from the retrospective studies are encouraging, the data from the prospective studies are important as these studies involved well-defined inclusion/exclusion criteria, careful patient selection via ^{68}Ga-PSMA-11 and FDG PET/CT imaging, and prespecified data collection and analysis (Emmett et al 2019, Violet et al 2020, Hofman et al 2021).

^{177}Lu-PSMA-617 treatment option is already recommended in the updated European treatment guidelines for the applied mCRPC population. However, no commercially available ^{177}Lu-PSMA-617 product is currently approved in the EU in a centralized procedure.

3.1.3. Main clinical studies

The **Pivotal Study PSMA-617-01** (VISION) is an international, prospective, open-label, multicenter, randomized Phase III study of 177Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC who were previously treated with 1-2 taxane-based chemotherapy regimens and at least 1 AR pathway inhibitor and who had a ^{68}Ga-PSMA-11 PET/CT scan that determined them eligible for inclusion. Patients were randomized in a 2:1 ratio to receive either 7.4 GBq (± 10%) 177Lu-PSMA-617 plus BSC/BSoC or to receive BSC/BSoC only.

3.2. Favourable effects

At the 27-Jan-2021 DCO with a median follow-up time for OS of ~20 months, both alternate **primary efficacy objectives** in the VISION study of rPFS and OS **were met** and their analyses are thus to be regarded as final.

In the PFS-FAS (see below), treatment with 177Lu-PSMA-617 showed a statistically significant improvement in **rPFS** compared with BSC/BSoC: HR = 0.40 (99.2% CI: 0.29, 0.57); $p < 0.001$; median rPFS 8.7 months (99.2% CI: 7.9; 10.8) vs. 3.4 months (99.2% CI: 2.4; 4.0).All performed sensitivity/supportive analyses for rPFS (including a sensitivity analysis in line with EMA guidance [EMA/CHMP/27994/2008/Rev.1]) support the rPFS primary analysis. Plus, subgroup analyses for rPFS were consistent with the primary rPFS analysis and demonstrated consistency of the treatment effect across clinically relevant subgroups.

In the FAS (see below), treatment with ^{177}Lu-PSMA-617 showed a statistically significant improvement in **OS** compared with BSC/BSoC: HR = 0.62 (95% CI: 0.52; 0.74); $p < 0.001$; median OS 15.3 months (95% CI: 14.2; 16.9) vs. 11.3 months (95% CI: 9.8; 13.5).All performed sensitivity/supportive analyses for OS support the OS primary analysis. Plus, subgroup analyses for OS were consistent with the primary OS analysis and demonstrated consistency of the treatment effect across clinically relevant subgroups.

Also for the **key secondary endpoints**, i.e. ORR, DCR and SSE, treatment with ^{177}Lu-PSMA-617 showed a statistically significant improvement compared with BSC/BSoC, see results in below Effects Table.

3.3. Uncertainties and limitations about favourable effects

Considering the lower recurrence rate of the PROs-Questionnaires and the open design, the reliability of the reported PRO results in favor of treatment with 177Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC is seen as low. In summary, it cannot be excluded that a positive effect on QoL is seen in ^{177}Lu-PSMA-617 treated patients, who well respond on the treatment, but not more.

Homogeneity and consistency of the alternate primary endpoints rPFS and OS was not demonstrated across subgroups of Asians, African Americans or Blacks, and baseline PSADT >9 months due to too few patients included.

3.4. Unfavourable effects

In comparison to BSC/BSoC, ^{177}Lu-PSMA-617 on top of BSC/BSoC treatment leads to more and pronounced safety risks. Overall, all relevant key safety characteristics (TEAEs, drug-related TEAEs, grade $\geqslant$3 events, as well as SAEs including fatal SAEs) occurred more frequent in the 177Lu-PSMA-617+BSC/BSoC arm. However, at least partially this effect is caused by the significantly shorter observation periode in the BSC/BSoC arm due to the higher drop-out rate in in the BSC/BSoC only arm. The resulting imbalance in treatment duration has biased the pivotal trial PSMA-617-01, but in disadvantage for ^{177}Lu-PSMA 617.

The higher rates of TEAEs and SAEs in general (PSMA:36.3% vs BSC: 27.8%) are probably mainly caused by the disease, as illustrated by the significantly lower rates of drug-related SAEs (PSMA: 9.3% vs BSC: 2.4%). Nevertheless, the higher overall SAE rate may at least partially reflect the additional toxicity associated with ^{177}Lu-PSMA-617 treatment. However, the longer duration of exposure to randomized treatment in the PSMA arm may have resulted in a bias which disadvantages ^{177}Lu-PSMA-617 also.

Grade ≥ 3 AEs were mainly restricted to hematological events, more adverse events were observed in patients receiving 177Lu-PSMA-617+BSC/BSoC (52.7%) vs. 38.0% of patients receiving BSC/BSoC only; however, the incidence of each individual grade ≥ 3 AE was low.

While 85 patients died while on-treatment (PSMA: 12.5% vs BSC: 9.3%) mostly due to disease progression (PSMA: 8.3% vs BSC: 6.8%). However, three deaths were reported to be related to study treatment by the Investigator: 2 deaths due to pancytopenia and 1 death due to bone marrow failure, all in the 177Lu-PSMA-617+BSC/BSoC arm only. In a trial with a comparison with BSC/BSoC this may be expected, but may indicate also a higher risk due to the additional treatment.

In total, 5.7% of the patients had TEAEs that led to dose reduction in the ^{177}Lu-PSMA-617 arm and 11.9% of the patients discontinued ^{177}Lu-PSMA-617 due to TEAEs. The most frequent TEAEs leading to discontinuation of ^{177}Lu-PSMA-617 were related to myelosuppression.

The greatest differences (≥20%) between the 2 treatment arms (177Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were observed for gastrointestinal disorders (PSMA: 75.4% vs BSC: 31.7% of patients), general disorders and administration site conditions (PSMA: 61.2% vs BSC: 38.5% of patients) and blood and lymphatic system disorders (PSMA: 47.8% vs BSC: 18.0% of patients). Moreover, probably in the context of the decrease leucocytes urinary tract infection were also more frequent (PSMA: 11.0% vs BCS: 1.0% patients).

Adverse events of special interest (AESIs) for ^{177}Lu-PSMA-617 were Fatigue (49.1% patients vs. 29.3% patients), Myelosuppression (47.4% patients vs. 17.6% patients), Dry Mouth (39.3% patients vs. 1.0% patients), Nausea and Vomiting (39.3% patients vs. 17.1% patients). These AESI are caused by the active anti-cancer treatment and are related to the known mechanism of action of 177Lu-PSMA-617.

Drug-related TEAEs (as assessed by the Investigator) were clearly more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm (85.3% patients) as compared to the BSC/BSoC only arm (28.8% patients) as could be expected. The high grade (≥3) events were reported with highest incidence in this arm for anemia (9.6% patients), thrombocytopenia and lymphopenia (6.8% each).

Dry mouth, fatigue and nausea, that were the most reported drug-related events in this arm, were usually low grade (≤2) in severity.

Myelosuppression: based on the sensitivity of the bone marrow to radiation effects, this is considered a known risk for ^{177}Lu-PSMA-617. Data from the PSMA-617-01 sub-study showed that the mean absorbed radiation dose for 177Lu-PSMA-617 in the red marrow was 0.035±0.020 Gy/GBq. As could be expected the frequency of myelosuppression-related events (including anemia, thrombocytopenia, lymphocytopenia, leukopenia, neutropenia) was consistently higher in the 177Lu-PSMA-617+BSC/BSoC arm (47.4% of patients) compared with the BSC/BSoC only arm (17.6% of patients). The most frequent myelosuppression-related adverse events were anemia, thrombocytopenia, lymphocytopenia, leukopenia and neutropenia, but were considered manageable with standard clinical interventions.

Renal toxicity is also increased due to PSMA expression in the proximal tubule and the known renal route of ^{177}Lu-PSMA-617 excretion and considered a known risk for ^{177}Lu-PSMA-617. Data from the PSMA-617-01 sub-study showed that the mean radiation absorbed dose for the kidneys was 0.43 ± 0.16 Gy/GBq. However, renal events in general were observed slightly more frequent with 8.7% of patients in the 177Lu-PSMA-617+BSC/BSoC arm than in the BSC/BSoC only arm (5.9%). However, the differences between renally impaired versus non-impaired groups were greater for high grade TEAEs (77.4% patients vs. 50.5% patients), and serious TEAEs (67.7% patients vs. 32.9% patients). Similar difference (50.0% patients vs. 26.4% patients) was noted in the BSC/BSoC only arm for the serious TEAEs. Moreover, the incidence of fatal TEAEs, though low in number overall, was 4 times more in the impaired group as compared with the non-impaired (12.9% patients vs. 3.0% patients) in the 177Lu-PSMA-617+BSC/BSoC arm and more than 2 times in the impaired group as compared with the non-impaired in the BSC/BSoC only treatment arm (7.1% patients vs. 2.7% patients). Therefore, subjects with a moderate renal impairment (CLcr <50 mL/min) may bear an inherent risk of increase in AEs and treatment with ^{177}Lu-PSMA-617 is not recommended in these patients.

In ^{177}Lu-PSMA-617 patients, renal toxicity was predominantly low-grade comprising creatinine increases that were manageable and reversible. Nevertheless, also grade ≥3 events occurred.

Hepatotoxicity was reported slightly higher for ^{177}-Lu-PSMA (PSMA: 10.2% vs. BSC: 7.8%), however, very few events led to withdrawal from 177Lu-PSMA-617+BSC/BSoC (0.6% patients).

Non-hematological TEAEs: Similarly, although the TEAEs such as dry mouth (38.8% vs 0.5%), nausea (35.3% vs 16.6%), diarrhea (18.9% vs 2.9%), vomiting (18.9 vs 6.3%) and urinary tract infections (11% vs 1%) were also more frequent in the 177Lu-PSMA-617+BSC/BSoC arm; however, they were usually low grade (≤2) in severity; and they only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤0.5% of patients. Moreover, the underlying disease or concomitant treatment with opioids may also have contributed this type of adverse events.

Despite the high apparent radiation exposure, incidences of **lacrimal toxicities, i.e. dry eye and blurred vision** were infrequent and were mostly low grade (grade 1-2) in the PSMA-617-01 study. Two (0.4%) patients in the 177Lu-PSMA-617+BSC/BSoC arm had high grade (≥3) events of blurred vision.

Second Primary Malignancies as consequence of the radiation were infrequent events in both arms (2.1% patients vs. 1.0% patient). The events were skin cancers and metastases to the brain or meninges. However, one case of acute myeloid leukemia (AML) was reported outside of the treatment-emergent period, after the 30-day post-treatment follow-up, but before capture of long-term follow-up events.

In total, 5.7% of the patients had TEAEs that led to dose reduction in the ^{177}Lu-PSMA-617 arm and 11.9% of the patients discontinued ^{177}Lu-PSMA-617 due to TEAEs. The most frequent TEAEs leading to discontinuation of ^{177}Lu-PSMA-617 were related to myelosuppression.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile derived from the pivotal study is not from ^{177}Lu-PSMA-617 given as monotherapy.

The open-label design of the pivotal study may have affected safety reporting.

Many of the more frequently reported adverse events are often observed in this patient population and may be related to the underlying disease and/or other comorbidities. Thus, identification of drug-related adverse events needs to consider the off-target tissues for ^{177}Lu-PSMA-617 mainly, but causality for other events remains difficult to assess at the end.

The impact of the significantly shorter treatment exposure (Median PSMA: 7.8 months vs BSC: 2.1 months) in the BSC/BSoC arm in comparison to treatment with ^{177}Lu-PSMA-617 on top of BSC/BSoC arm for safety regarding the higher frequency and grading of adverse events was probably relevant. However, since the time in which TEAEs were registered was significantly longer, event rates are clearly skewed in disadvantage for 177-Lu-PSMA. In general, this seems to be confirmed by the reported exposure-adjusted adverse event rates that were submitted.

The imbalance of drug-related AEs, as assessed by the Investigator, needs to be interpreted with caution as the study was open-label. Moreover, patients were already receiving BSC/BSoC before randomization and standard of care might have not been systematically considered as Study Drug by some Investigators.

The uncertainty that there may be a potential for ameliorated tolerability at a lower dose level remains. However, it is unknown whether this would maintain similar clinical benefit.

Myelosuppression events in the ^{177}Lu-PSMA-617 arm occurred frequently and these events have a large impact on the toxicity, tolerability and on treatment-related deaths. It is unclear whether risk minimalization measures were taken/were effective on this subject.

Based on the available data/modelling from the ECG sub-study a QT prolongation above 10 ms cannot be excluded and in this situation additional evaluation by ECG and PK samples in clinical studies would have been needed, however such data has not been collected. There were no patients observed to have had Torsade de pointes. It remains uncertain that ^{177}Lu-PSMA-617 does not influence the QT interval. The Applicant was recommended to perform a QTc (sub)study as part of post-authorisation Study CAAA617A12202.

The risk of haematological malignancies particularly for leukemia/MDS and other malignancies is clearly a well-known complication of all types of radiation treatment and probably beside the risks derived from bone marrow impairment (Bleeding, Infection) the most severe adverse event of RLT. A case of AML is already reported. However, it is acknowledged that in an advanced mCRPC population with a limited life-expectance the relevance of these events may be probably balanced by the improvement in overall survival. As in other RLTs before this important risk remains not fully evaluable from the data submitted, but the applicant as committed to provide further data during longer follow-up.

It is not known whether AEs related to the safety topics resolved over time as these data were not collected by the Applicant. The applicant has meanwhile committed that these data will be submitted at the time they become available via the post-marketing requirement (PMR) of the FDA, which is intended to collect data on risks of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications, and potential of secondary malignancies.

3.6. Effects Table

Table 24: Effects Table for lutetium (^{177}Lu) vipivotide tetraxetan (Data cut-off date: 27-Jan-2021).

Effect	Short Description	Unit	Treatment ^{177}Lu-PSMA-617+BSC/ BSoC arm	Control BSC/BSoC only	Uncertainties/ Strength of evidence	Refer-ences
Favourable Effects						
rPFS	Radiographic progression-free (or death from any cause) survival	Months	8.7 months (99.2% CI: 7.9, 10.8)	3.4 months (99.2% CI: 2.4, 4.0)	An estimated 60% reduction in the risk of radiographic disease progression or death (HR = 0.40; 99.2% CI: 0.29, 0.57; log-rank 1-sided p-value < 0.001)	CSR PSMA-617-01
OS	**Overall Survival**	months	15.3 months (95% CI: 14.2, 16.9)	11.3 months (95% CI: 9.8, 13.5)	OS prolongation of 4.0 months corresponding to an estimated 38% reduction in the risk of death (HR = 0.62; 95% CI: 0.52, 0.74; log-rank 1-sided p-value < 0.001)	CSR PSMA-617-01
ORR	Objective response rate (ORR) (CR + PR); RECIST v1.1	%	29.8%	1.7%	Odds ratio of 24.99 (95% CI: 6.05, 103.24). The response was durable in the 177Lu-PSMA-617+BSC/BSoC arm: median of 9.8 months (95% CI: 9.1, 11.7)	CSR PSMA-617-01

Effect	Short Description	Unit	Treatment ^{177}Lu-PSMA-617+BSC/ BSoC arm	Control BSC/BSoC only	Uncertainties/ Strength of evidence	Refer-ences
DCR	Disease Control Rate (DCR) (CR + PR + stable disease [SD]) as measured by RECIST v1.1	Odds ratio	89.0%	66.7%	Odds ratio of 5.79 (95% CI: 3.18, 10.55)	CSR PSMA-617-01
Time to SSE	The time to a first SSE (first new symptomatic skeletal event or death due to any cause)	Median Delay in Months	11.5 months (95% CI: 10.3, 13.2)	6.8 months (95% CI: 5.2, 8.5)	The median time to SSE was delayed by 4.7 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm.	CSR PSMA-617-01
Unfavourable Effects						
Drug-related SAE	Drug-related Serious adverse event	% per arm	9.3%	2.4%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01
Drug-related grade 3/4/5 TEAE	Treatment-emergent adverse event	% per arm	28.4%	3.9%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01
Grade ≥ 3 adverse events		% per arm	52.7%	38.0%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01
Myelosup-pression	Adverse events associated with myelosuppression (all grades)	% per arm	47.4%	17.6%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01
Renal toxicity	Renal adverse events	% per arm	8.7%	5.9%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01

Effect	Short Description	Unit	Treatment ^{177}Lu-PSMA-617+BSC/ BSoC arm	Control BSC/BSoC only	Uncertainties/ Strength of evidence	Refer-ences
GI-adverse events	Nausea Vomiting Diarrhea	% per arm	35.3% 18.9% 18.9%	16.6% 6.3% 2.9%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01
Dry mouth	Glandular toxicity	% per arm	38.8%	0.5%	Due to short follow-up (30 day) and lower exposure than 6 cycles in 53.5 % of trial population probably higher in real world	CSR PSMA-617-01

Notes: limited data from Asian (2.4% of patients overall) or African American or Black (6.6%) patients from Study PSMA-617-01.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Even though approved treatments exist for (at least) part of the target population, it is noted that patients with mCRPC who have previously received a NAAD as well as taxane-based chemotherapy have few therapeutic options. ^{177}Lu-PSMA-617 has a new and different mechanism of action and could, therefore, be considered a welcome addition to the treatment armamentarium.

In the pivotal study VISION, treatment with ^{177}Lu-PSMA-617 showed an improvement in both primary endpoints of rPFS by BICR and OS compared with treatment with BSC/BSoC, of which the OS benefit is considered clinically relevant. The OS data/results are considered sufficiently mature for B/R assessment and are considered robust, as all performed sensitivity/supportive analyses support the OS primary analysis and all subgroup analyses for OS provided results consistent with this analysis. The rPFS result and the results for the key secondary endpoints (ORR, DCR, and SSE) are considered to provide support for the OS result.

The design of the VISION study was amended several times (as was the SAP), in part in reaction to a higher than anticipated rate of patients withdrawing from the control arm in the early part of the study. Even though the Applicant did not (fully) comply with SA given on this matter, this is acceptable/accepted because the primary endpoint OS is considered to be an objective, 'hard' endpoint and the OS data/results are considered robust.

The improved efficacy should be weighed against a more unfavourable safety profile compared with BSC/BSoC alone. This is exemplified by higher numbers of all-causality and treatment-related AEs, severe AEs, SAEs and treatment-related deaths. Noteworthy are the AEs of myelosuppression which are mostly treatment-related and are the main causes of severe AEs, SAEs, treatment-related deaths and tolerability issues.

3.7.2. Balance of benefits and risks

In patients with progressive, PSMA-positive mCRPC, who had received ≥ 1 NAAD and had previously been treated with 1-2 taxane-based chemotherapy regimens, treatment with ^{177}Lu-PSMA-617 showed a statistically significant and clinically relevant improvement in OS compared to treatment with BSC/BSoC. The safety profile of ^{177}Lu-PSMA-617 although non-negligible, it is outweighed by the compelling efficacy outcomes. It can be agreed that the benefit/risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

In line with the Guidance "Wording of therapeutic indication - A Guide for Assessors of Centralised Applications" (EMA/CHMP/483022/2019) "*in combination with androgen deprivation therapy (ADT) with or without androgen receptor (AR) pathway inhibition*" has been added to the indication wording based on the following considerations:

- "*in combination*" includes all anti-cancer medicinal products that patients in the VISION study received and by the term "ADT" also encompasses surgical castration;
- "*with or without*" correctly reflects that AR pathway inhibition was not mandatory, but that over half of the patients (52.6% vs. 67.8%) received AR pathway inhibition (by a NAAD such as e.g. enzalutamide, abiraterone, apalutamide) in the VISION study as part of BSC/BSoC.
- The reference to section 5.1 will guide the prescriber to the relevant information on all medicinal products that were required and/or allowed as part of BSC/BSoC in the VISION study.

Furthermore, it was acknowledged that previous treatment with AR pathway inhibition and taxane-based chemotherapy can occur at any time during the management of the disease and treatment of prostate cancer.

3.8. Conclusions

The overall benefit/risk balance of Pluvicto is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pluvicto is favourable in the following indication:

Pluvicto 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).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Pluvicto in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient guide, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The patient guide is aimed to reduce the risk of inadvertent radiation exposure.

The MAH shall ensure that, in each Member State where Pluvicto is marketed, patients have access to the patient guide.

The Pluvicto patient guide contains the following key elements:

- What Pluvicto is and how it works
- Description of risk guidance on:
  - Hydration
  - Close contacts
  - Care givers
  - Sexual activity and contraception
  - Toilet use
  - Showering and laundry
  - Waste disposal

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lutetium (^{177}Lu) vipivotide tetraxetan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.