Clinical Development

lutetium (^{177}Lu) vipivotide tetraxetan

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

Module 2.7.4 Summary of Clinical Safety in prostrate-specific membrane antigen-positive metastatic castration-resistant prostrate cancer

Document type:	CTD Clinical summary document
Document status:	Final
Release date:	13-Sep-2021

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List of abbreviations used in the text

^{68}Ga-PSMA-11	Gallium-labeled PSMA-11
^{177}Lu-PSMA-617	Lutetium-labeled PSMA-617
AAA	Advanced Accelerator Applications
AE	Adverse Event
AESI	Adverse Event of Special Interest
APCCC	Advanced Prostate Cancer Consensus Conference
ARI	Androgen Receptor Inhibitors
ASCO	American Society of Clinical Oncology
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BCRP	Breast Cancer Resistance Protein
BILI	Bilirubin
BSA	Body surface area
BSC/BSoC	Best Supportive/Best Standard of Care
CNS	Central Nervous System
CI	Confidence Interval
COVID-19	Corona virus disease 19
CR-EDTA	Chromium Ethylenediaminetetraacetic Acid
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DKFZ	German Cancer Research Center
DOTA	Dodecane tetraacetic acid
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Extended release
ESMO	European Society for Medical Oncology
eGFR	Estimated Glomerular Filteration Rate
FAS	Full Analysis Set
ITT	Intention-To-Treat
LDH	Lactate Dehydrogenase
MATE	Multidrug and Toxin Extrusion
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NAAD	Novel Androgen Axis Drug
NCI	National cancer institute
NCCN	National Comprehensive Cancer Network
NOAEL	The no-observed-adverse-event level
OS	Overall Survival

OAT1	Organic Anion Transporters
OATP	Organic Anion Transporting Polypeptides
OCT	Organic Cation Transporters
PC	Prostate Cancer
PCWG3	Prostate Cancer Working Group 3
PET	Positron Emission Tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PSA	Prostate-Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
PT	Preferred Term
QoL	Quality of Life
RLT	Radioligand Therapy
SAE	Serious Adverse Event
SCS	Summary of Clinical Safety
SCP	Summary of Clinical Pharmacology
SD	Standard Deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SSE	Symptomatic Skeletal Event
TEAE	Treatment Emergent Adverse Event
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
US	United States of America
UTI	Urinary Tract Infection
WHO	World Health Organization

1 Exposure to the drug

1.1 Overall safety evaluation plan and narratives of safety studies

1.1.1 Safety aspects of the product and targeted indication

1.1.1.1 Product and targeted indication

Globally, prostate cancer (PC) is the second most common cancer in men and the 5th 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). In the US, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (American Cancer Society 2020); in Europe, 473,344 new cases and 108,088 deaths were estimated for 2020 (International Agency for Research on Cancer 2020).

PC is the second leading cause of cancer-related death among men in the United States, and the third leading cause of cancer-related death among men in Europe (Malvezzi et al 2019, Siegel et al 2020).

Early-stage PC can often take on an indolent clinical course and an asymptomatic manner, however, once metastasized, PC becomes more aggressive often leading to significant bone pain and clinical management difficulties. These facts underscore the seriousness of the mCRPC diagnosis and indicate an urgent need for new and effective treatments for patients.

Ten to 20% of patients with PC become castration-resistant within 5 years and > 50% of them die within 3 years with historical standard therapies (Nussbaum et al 2016). Once patients reach the metastatic castration-resistant prostate cancer (mCRPC) stage, their expected overall survival is low (Smith et al 2016). Hence, alternative therapeutic options such as systemic radioligand therapy (RLT) for men with mCRPC are urgently needed.

Over the past several decades, numerous theranostic approaches based on the use of a radioligand imaging agent and radioligand therapy (RLT) were designed to target receptors on the cancer cell surface. Antibodies (whole or small fragments), small molecules, peptides with affinities to receptors (agonist or antagonist) have demonstrated *in vivo* efficacy for targeting cancers based on up-regulated antigens or receptor populations. RLT presents several advantages over conventional chemotherapy, including an opportunity for patient selection and for a targeted therapeutic approach. The expression of the tumor-specific antigen or receptor can be identified by a diagnostic probe before exposing patients to therapeutic doses of these agents allowing identification of suitable subjects for therapeutic procedures and preventing unnecessary exposure of the patients to radiation without significant benefit. This approach allows the physician to select only those patients with suitable expression of the target prior to treatment. Since the RLTs accumulate mainly in the tumor tissue and the unused radioactive materials are excreted from the body, this targeted treatment strategy is generally well tolerated.

Overall, targeted RLT offers the possibility to treat the PC lesions in a specific and tumor-selective manner by exploiting cell surface receptors mainly expressed on malignant cells. The prostate-specific membrane antigen (PSMA) is thus a potential target for PC therapy because it is highly expressed in PC, including mCRPC.

Prostate-specific membrane antigen

PSMA is a type II transmembrane protein that is highly expressed in PC, including mCRPC, but it has several hundred-fold lower and restricted expression in normal tissues such as normal prostate, salivary glands, renal tubular cells, and small intestine (Bostwick et al 1998, Ghosh and Heston 2004, Mannweiler et al 2009).

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

The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using radioactive imaging as well as therapeutic intervention, and therefore may be an attractive target for patients with mCRPC. Because of the low and restricted expression levels in normal tissues, PSMA has the potential to be a viable target for RLT with minimized radioactivity-related side effects.

In addition to the expression pattern, the functionality of PSMA plays an equally important role in its value as a tumor-specific targeting mechanism. Specifically, the binding of a high affinity ligand to PSMA, such as the targeting moiety in ^{177}Lu-PSMA-617, leads to internalization through endocytosis and a sustained retention of the ligand and its bound radioactive cargo within the cancer cell (Rajasekaran et al 2003).

PSMA-targeted RLT utilizes radiolabeled small molecules which bind 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 lesions.This functional feature of PSMA allows for the development of low-molecular-weight targeted radiopharmaceuticals with favorable pharmacokinetic and tumor penetration properties (Haberkorn et al 2016).

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

For the purposes of this document, the radioactive diagnostic agent gallium (^{68}Ga) gozetotide (AAA517/ [^{68}Ga]Ga-PSMA-11), is referred to as ^{68}Ga-PSMA-11; and the therapeutic agent lutetium (^{177}Lu) vipivotide tetraxetan (AAA617/[^{177}Lu]Lu-PSMA-617), is referred to as ^{177}Lu-PSMA-617.

^{177}Lu-PSMA-617 in advanced prostate cancer

The therapeutic drug ^{177}Lu-PSMA-617 is a novel small molecule PSMA-targeted RLT that takes advantage of the unique attributes of PSMA. As described above, and with the recent data, ^{177}Lu-PSMA-617 has been shown to deliver clinical benefit and can advance the manner in which PC is treated. This drug was developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg for the treatment of patients with mCRPC.

PSMA-617, the nonradioactive precursor molecule which consists of the PSMA-binding ligand glutamate-urea-lysine and a DOTA-chelator, which are connected by a linker moiety. ^{177}Lu, a radioactive therapeutic agent is delivered to the cancer cell by the precursor molecule PSMA-617. ^{177}Lu has physical properties that make it an ideal radionuclide for the treatment of mCRPC. ^{177}Lu 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, Emmett et al 2017).

^{177}Lu-PSMA-617 has a high PSMA binding affinity and shows specific internalization into PSMA-positive cells for the treatment of mCRPC (Hillier et al 2009, Kratochwil et al 2015). Additionally, it has prolonged tumor retention, and rapid kidney clearance (Benešová et al 2015). Once endocytosed, the radioactive atom continues to decay with the additional advantage of irradiating 'bystander' cells.

Dosimetry data from literature have confirmed these findings that ^{177}Lu-PSMA-617 exhibits high and prolonged PSMA-specific tumor uptake, rapid background clearance, and fast kidney excretion, which gives clinical advantages for efficient RLT of recurrent PC (Benešová et al 2015, Delker et al 2016, Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017, Yadav et al 2017, Maffey-Steffan et al 2020). These physical properties of ^{177}Lu-PSMA-617 allow for short inpatient disposition, and reduced therapy-related toxicity (Delker et al 2016).

1.1.1.1.1 Patient population

After an initial response to androgen deprivation therapy by chemical and/or surgical castration, most patients with metastatic disease progress to mCRPC. Patients with mCRPC have a poor prognosis and their expected overall survival is low (Smith et al 2016). The median age at diagnosis of mCRPC is 70 years (Flaig et al 2016). Most of these patients at an advanced disease stage at an elderly age are already burdened by multiple medical therapies, such as chemotherapy, androgen deprivation therapies, and external beam radiotherapy, and as they exhaust existing treatment options, it leaves them with very few therapeutic options.

The available therapies and therapeutic developments with cytotoxic therapies have a negative impact on quality of life, and a high humanistic burden remains for patients with mCRPC. Symptomatic skeletal events (SSEs), comorbidities, and bone metastasis further add to the burden for these patients (Saad et al 2004, Kirby et al 2011). Almost all patients with PC ultimately progress and exhaust existing treatment options. High discontinuation rates and toxicities with current treatments along with low survival rates demonstrate there is still a profound need for new treatment options with significant antitumor activity and less toxicity for the treatment of heavily pretreated frail, elderly patients with mCRPC.

Available therapies and unmet need for target indication:

The current standard of care in metastatic PC is based on chemotherapy, androgen deprivation by different mechanisms of action on the hypothalamic-pituitary-gonadal axis, and adrenal-androgen receptor signaling.

Standard neuadjuvant androgen deprivation therapies and novel androgen axis drugs (NAADs) are commonly well tolerated and can stabilize mCRPC for many years. However, most patients with PC eventually progress to mCRPC, which remains challenging to treat. For purposes of this SCS, AR pathway inhibitors are considered synonymous with NAADs, and are referred to as NAAD in this SCS.

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 treatment with NAADs (i.e, abiraterone acetate or enzalutamide).

In clinical practice, abiraterone acetate or enzalutamide are often used in the first-line mCRPC setting. Sipuleucel-T is most commonly used in mildly asymptomatic small-volume disease, while ^{223}Ra dichloride is used to treat patients with bone-only disease. Taxane-based chemotherapy (i.e. docetaxel and cabazitaxel) is used after NAADs (abiraterone acetate or enzalutamide) 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 of these 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 the second-line of therapy.

A second-line therapy with 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, Badrising et al 2016, 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.

Though the treatment of PC and mCRPC has broadened over the last several years based on the approval of new agents including NAADs (particularly abiraterone and enzalutamide) and their use as first or second-line of treatment; however, these agents lose their effectiveness eventually, or result in intolerable toxicities, including neuropathy and bone marrow suppression, leaving the patients with advanced mCRPC with few therapeutic options (Sartor et al 2018).

Although the rate of PC and deaths has decreased over the period of time worldwide, PC remains the second most common cancer in males globally (Sung et al 2021).

In summary, although the therapeutic landscape of mCRPC has broadened over the last decade, there are still 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 already been used in earlier lines of therapy to manage the disease. Thus, this leaves this patient population with a high unmet medical need for novel treatment options.

Hence, given the promising published clinical evidence available at the time of registration study inception, it was hypothesized that treatment with ^{177}Lu-PSMA-617 plus best supportive care/best standard of care (BSC/BSoC) would provide therapeutic benefit for patients with mCRPC who had received prior at least 1 prior NAAD, and at least 1 prior taxane-based chemotherapy, and whose disease expressed PSMA as determined by ^{68}Ga-PSMA-11 PET/CT scan.

^{68}Ga-PSMA-11 was used to select patients with mCRPC for whom PSMA-targeted therapy with ^{177}Lu-PSMA-617 was indicated. For this submission, the safety profile of ^{68}Ga-PSMA-11 is not in scope and a separate submission is planned.

The purpose of this SCS is to provide a safety evaluation of lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu-PSMA-617), a RLT, for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC).

1.1.1.1.2 Known safety issues

Background:

To date, many studies with ^{177}Lu-PSMA-617 (dosimetry, retrospective, and prospective) have been conducted and the results published. These studies report promising results for response rates and a well-tolerated and manageable safety profile of ^{177}Lu-PSMA-617 in patients with mCRPC.

Clinical experience with ^{177}Lu-PSMA-617 (both retrospective and prospective studies) is documented in over 60 publications summarizing safety and or efficacy information from over 1900 patients treated with ^{177}Lu-PSMA-617.

Some of these publications provide clinically relevant in-depth AE data and patient population characterization at baseline (Rahbar et al 2016a, Rahbar et al 2016b, Bräuer et al 2017, Hofman et al 2017, Rahbar et al 2017, Hofman et al 2018). In recent years, prospective studies have confirmed the safety and efficacy reports from the previous prospective and retrospective studies, and provide further relevant clinical scientific evidence of the safety and/or efficacy of ^{177}Lu-PSMA-617 (Emmett et al 2019, Violet et al 2020, Hofman et al 2021).

To note, these publications report data from different patient populations in terms of baseline conditions, pre-treatments and concomitant medications, and multiple sources of origin of the active treatment product. However, despite these varying conditions, the literature overall suggests a well-tolerated safety profile for ^{177}Lu-PSMA-617.

Safety concerns:

Based on the published dosimetry study results, and the published clinical observations to date, the expected toxicities following ^{177}Lu-PSMA-617 therapy related to radiation damage to normal tissues that have PSMA expression; those that may be sensitive to transient radiation exposure; or those that are adjacent to tumor sites; those that may be involved in clearance. The safety concerns of ^{177}Lu-PSMA-617 therapy may therefore include the effects of radiological toxicity, namely xerostomia (dry mouth), fatigue, dry eyes, myelosuppression or hematological toxicities, nausea and vomiting, and renal effects (Rahbar et al 2016a, Rahbar et al 2016b, Bräuer et al 2017, Rahbar et al 2017, Yordanova et al 2017, Hofman et al 2018, Maffey-Steffan et al 2020, Violet et al 2020, Hofman et al 2021).

The safety observations from the published studies are summarized below.

Most frequently reported non-hematologic toxicities from the literature: The most frequently reported non-hematologic AEs of ^{177}Lu-PSMA-617 are dry mouth, nausea and vomiting, decreased appetite, pain, and fatigue. Most of these events appear to be non-specific (except dry mouth), and may be attributed to the administration of therapeutic levels of a radioactive compound.

Frequently reported hematologic toxicities or events related to myelosuppression from the literature: The most frequently reported hematologic AEs of ^{177}Lu-PSMA-617 are anemia, thrombocytopenia, leukopenia, lymphopenia, and neutropenia. No case of febrile neutropenia

has been reported in the literature. These events may be the result of significant bone marrow impairment at baseline. The risk of hematological toxicity or myelosuppression is greatest in those who have been heavily pretreated and have extensive marrow involvement.

Less frequently reported toxicities from the literature: The less frequently reported AEs of ^{177}Lu-PSMA-617 are dry eyes, anorexia, pain, diarrhea, dysgeusia, renal failure, pulmonary embolism, increase in ALP, AST or ALT, blood creatinine increase, and estimated glomerular filtration (eGFR) rate decrease.

Organs of special interest and related toxicities: Dosimetry studies have confirmed that the the normal tissues with the highest radiation absorbed dose following administration of ^{177}Lu-PSMA-617 are the salivary glands, kidneys, and lacrimal glands (Delker et al 2016, Kratochwil et al 2016, Kabasakal et al 2017, Scarpa et al 2017, Yadav et al 2017, Maffey-Steffan et al 2020). Hence, these organs are of special interest. The bone marrow is also of interest due to the presence of extensive PC bone metastases and prior therapies in the mCRPC population that can reduce the normal capacity of bone marrow function. While PSMA is not expressed in healthy bone marrow, this tissue is commonly radiosensitive due to its proliferative nature, and mCRPC patients typically have a high rate of bone disease, therefore some hematologic toxicity is to be expected due to transient radiation exposure or crossfire from targeted sites of disease. See Section 2.1.5.1.2 and [SCP-Section 3.3.2].

- **Salivary glands:** Dry mouth is frequently reported as reversible grade 1 or 2. The highest incidence of reversible grade 1/2 dry mouth (87% patients) was reported in the Hofman prospective Phase II LuPSMA study (Hofman et al 2018). There are no reports of grade >2 dry mouth in any published safety series.
  The salivary glands are a highly radiosensitive organ, therefore absorbed radiation dose limits for external beam radiation therapy (EBRT) induced salivary gland damage have been well-defined and dose-related (Grundmann et al 2009, Deasy et al 2010). However, unlike EBRT, RLT with Lutetium-177 has the biological advantage of delivering low dose rate beta radiation which maximizes the opportunity for normal tissue repair and minimizes late radiation damage.
  Clinical studies with ^{177}Lu-PSMA-617 to date seem to support this, demonstrating predominantly grade 1/2 reversible dry mouth. The absorbed radiation dose to the salivary glands following ^{177}Lu-PSMA-617 treatment is approximately 0.5-1.5 Gy/GBq, which has been associated with the relatively low severity and incidence of this AE. It has been suggested that a ^{177}Lu-PSMA-617 total cumulative dose 50 GBq could be administered without long-term salivary gland toxicity (Virgolini et al 2018).
- **Kidney:** To date, renal toxicity in ^{177}Lu-PSMA-617 clinical studies has not been notable in both frequency and severity. 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. Only one study has reported nephrotoxicity changes from grade 2 to grade 3 (occurring in 9.4% (3/32) of patients) (Maffey-Steffan et al 2020). Another study reported 2 cases (2, 16.7% patients) of grade 3/4 nephrotoxicity (Beytur et al 2020).
  In the Hofman prospective Phase II LuPSMA study, grade 1-2 renal injury occurred in 10% of patients. There was a mean decline of 51Cr-EDTA eGFR of 11.7 mL/min (95% CI -19 to -4 mL/min) 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-61 could be as high as 61.66+/-35.97 GBq.

Current published clinical data do not show renal toxicity to be an important safety concern during treatment with ^{177}Lu-PSMA-617 and the long-term follow-up, but due to the possibility of radiotoxic damage to this exposed tissue, renal toxicity may still present a risk in months to years following treatment.

- **Lacrimal glands:** Radiation exposure of ^{177}Lu-PSMA-617 to the lacrimal glands have only been reported in some studies in the literature (range 0.85±0.51 Gy/GBq to 1.23±0.70 Gy/GBq) reported in publications from Delker et al (2016), Kratochwil et al (2016), Kabasakal et al (2017), Scarpa et al (2017), Yadav et al (2017), Kamaldeep et al (2021), and Maffey-Steffan et al (2020). Higher ranges (mean 2.1 Gy/GBq and range 0.36-3.8 Gy/GBq) were also reported in publications from Hohberg et al (2016) and Violet et al (2019). See [SCP- Section 3.3.2]). As per data from dosimetry studies, the largest radiation absorbed dose is in the lacrimal glands. However, so far, only low frequency and low-grade AEs of dry eye were reported from literature (Hofman et al 2018, Hofman et al 2021). Lacrimal gland exposure limits have not routinely been considered when applying dosing parameters to treatment with ^{177}Lu-PSMA-617, and while not considered a dose-limiting organ with regard to dose selection, the distribution to this tissue needs to be monitored more closely to assess the risk of toxicities.
- **Bone marrow:** The bone marrow is also of interest due to the presence of extensive PC bone metastases and prior therapies in the mCRPC population that can reduce the normal capacity of bone marrow function. The risk of hematological toxicity is greatest in those who have been heavily pre-treated and have extensive marrow involvement that can reduce the normal capacity of bone marrow function. The published dosimetry studies with ^{177}Lu-PSMA-617 showed that the average bone marrow absorbed radiation doses are low unless there is a large burden of metastatic disease in the bone marrow. The levels of radiation in the non-diseased bone marrow are low due to the lack of PSMA expression in this tissue, and the rapid clearance of ^{177}Lu-PSMA-617 from systemic circulation. Radiation absorbed dose limits have been defined for EBRT induced hematological damage at 2 Gy. However, radiobiological estimation of a tolerable ^{177}Lu-PSMA-617 cumulative dose for bone marrow has been suggested to be 45 to 73 GBq (Kabasakal et al 2017, Scarpa et al 2017). Scarpa et al (2017) also noted that higher activity and shorter treatment intervals should be applied to increase efficacy and noted that cumulative dose of 30 GBq adminsitered every 6 to 10 weeks was safe especially considering the dose to kidney and bone marrow (Scarpa et al 2017, Virgolini et al 2018).

Summary of known safety observations from literature:

- The observed toxicities to date appear to be predominantly grade 1/2, reversible, and most frequently seen as salivary gland, hematological and gastrointestinal toxicity.
- The incidence of grade 3/4 toxicities is very low, and mainly restricted to reversible hematological events.
- Reversible hematological toxicity is noted following ^{177}Lu-PSMA-617 treatment that manifest as leukopenia and thrombocytopenia. In most clinical series this was an increase over baseline.
- Frequent hematologic toxicities or myelosuppression related events noted are anemia, thrombocytopenia, lymphopenia, leukopenia, and neutropenia, which may be due to

significant bone marrow impairment at baseline. No case of febrile neutropenia was reported in literature.

- On-target toxicities:
  - Dry mouth is reported as reversible grade 1/2, with no reports of >grade 2 dry mouth in any published safety series. Reversible grade 1/2 dry eyes have been reported much less frequently.
  - Nephrotoxicity has not been notable in any safety series. Only one study has reported nephrotoxicity changes from grade 2 to grade 3; and 2 cases of grade 3/4 nephrotoxicity have been reported in the literature (Beytur et al 2020).
- Most frequent non-hematological toxicities associated with ^{177}Lu-PSMA-617 treatment are nausea, vomiting, dry mouth, decreased appetite, pain and fatigue. These are non-specific and may be attributed to the administration of therapeutic levels of a radioactive compound.

1.1.2 Sources of safety data and safety evaluation plan

1.1.2.1 Clinical studies in the target indication

An overview of the 2 studies (PSMA-617-01 and PSMA-617-02) that primarily contributed to the safety analysis for this submission is provided in Table 1-1.

The main safety evaluation was based on data from the registration study PSMA-617-01 (VISION); and a supportive study PSMA-617-02 (RESIST-PC), which were both performed in the target indication of mCRPC. In this safety analysis, results are presented by individual studies. In the 2 studies, the FAS safety analysis set was defined as all patients who received at least 1 dose of ^{177}Lu-PSMA-617. Only the subgroup analyses from the PSMA-617-01 study are being discussed in this SCS. See Section 5 for safety assessments in special groups and sitiations.

The PSMA-617-01 main study included a sub-study in which 30 additional patients received ^{177}Lu-PSMA-617, outside of the randomization, in order to assess PK, dosimetry, ECG and urinalysis data. Results from these 30 patients are reported separately from the FAS safety analysis set. Limited exploratory ER analyses were performed for exposure/dosimetry and acute toxicity related to kidney, bone marrow, salivary and lacrimal glands during the first cycle of treatment with ^{177}Lu-PSMA-617. See [SCP-Section 3.3.2] for the results from the sub-study.

1.1.2.1.1 Analysis Sets PSMA-617-01 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.

FAS Safety Analysis Set: The subset of patients in the FAS who received at least 1 dose of randomized therapy. Patients were included in the treatment arm corresponding to the actual treatment received.

The safety assessments consisted of TEAEs, ECGs (at screening in the sub-study only), laboratory data, exposure and vital signs. Specific safety subgroups were planned for this submission. See Section 5.

1.1.2.1.2 Analysis Sets PSMA-617-02 study

ITT population: All patients who signed ICFs were randomized and constituted the ITT population. Patients were included in the treatment arm to which they were randomized regardless of actual treatment received. Patients who failed screening, i.e., were not eligible based on inclusion/exclusion criteria (screen failures), and patients who withdrew consent during the screening period were still randomized and were part of the ITT population.

Safety Analysis Set (SAS): The subset of patients in the ITT population, who received at least one dose of randomized therapy constituted the SAS. Patients were included in the treatment arm corresponding to the actual treatment received.

The safety assessments consisted of AEs, laboratory data, and vital signs.

This study was ongoing when Endocyte acquired global development rights to PSMA-617. After the acquisition of PSMA-617, Endocyte re-evaluated the clinical development plan for PSMA-617, and consequently, the PSMA-617-02 study was terminated early (enrollment ended as of 22 Jun 2018). The early termination and the missing data resulted in a significantly smaller sample size (64 patients) in the safety population than initially planned. All patients who had been identified to Endocyte as "engaged" as of 22 June 2018 were allowed to continue the screening process through 31 July 2018. All patients that were enrolled in the PSMA-617-02 study continued to follow the protocol visit schedule through to completion of the study.

PSMA-617-02 study provides supportive safety information for this submission [Study PSMA-617-02].

The 2 clinical studies PSMA-617-01, and PSMA-617-02 that contributed to the safety analysis are summarized in the [Tabular Listing of All Clinical Studies], and presented according to their design or purpose. See Table 1-1 for an overview of the 2 studies. Details of the safety analysis for each study are presented in the individual CSRs.

Table 1-1 Clinical studies with ^{177}Lu-PSMA-617 that contributed to the safety analysis

	Registration study	Supportive study
Study	**PSMA-617-01 (VISION)**	**PSMA-617-02 (RESIST-PC)**
Phase	3	2
Population studied	Men with progressive PSMA-positive mCRPC who received at least one NAAD and 1 to 2 taxane-based chemotherapy regimens	Men with progressive PSMA-positive mCRPC after at least one NAAD and either chemotherapy naïve or post-chemotherapy
^{177}Lu-PSMA-617 dose and frequency	7.4±10% GBq IV every 6 weeks for a maximum of 6 cycles	6.0±10% GBq (Arm 1) or 7.4±10% GBq (Arm 2) IV every 8 weeks until reaching 4 cycles or threshold maximum dose to the kidneys of 23 Gy as determined by dosimetry
Treatment Groups	Investigational arm: 7.4 GBq ^{177}Lu-PSMA-617+BSC/BSoC Control arm: BSC/BSoC only	Arm1: 6.0 GBq ^{177}Lu-PSMA-617 Arm 2: 7.4 GBq ^{177}Lu-PSMA-617
Number of patients	N=734 (FAS Safety Analysis Set) Investigational arm: N=529 Control arm: N=205	N=64 (SAS) Arm 1: N=23 Arm 2: N=41
FPFV	29-May-2018	05-Jul-2017
Data cut-off	27-Jan-2021	15-Jan-2020

Source: [Study PSMA-617-01] and [Study PSMA-617-02]

1.1.2.2 Summary of pertinent non-clinical data

Safety pharmacology and toxicology studies have been conducted using either a test solution (containing non-radioactive labeled ^{175}Lu-PSMA-617/unlabeled PSMA-617 in a ratio of around 1:1) as a non-radioactive surrogate of ^{177}Lu-PSMA-617; or using unlabeled PSMA-617 alone.

No toxicologic effects related to the single-dose intravenous (iv) administration of the test solution were observed in Sprague Dawley rats at the doses of 2.0 and 4.0 mg/kg. The No Observed Adverse Effect Level (NOAEL) for this study in rats was considered the highest tested dose (4.0 mg/kg), which corresponds to a dose approximately 150-fold higher than the maximum human PSMA-617 ligand dose (275 µg) based on body surface area (BSA) scaling.

No systemic toxicologic effects related to the single-dose iv administration of the test solution were observed in Göttingen minipigs at the doses of 0.2, 0.6 and 1.8 mg/kg. The dose of 1.8 mg/kg is considered the NOAEL for this study. This dose corresponds to a dose approximately 400-fold higher than the maximum human PSMA-617 ligand dose (275 µg) based on BSA scaling. Locally, minimal or mild acute inflammation associated with vascular and perivascular necrosis occurred in animals treated at all doses 1 day after administration. Fourteen days after administration, these changes were still present, even if with a recovery trend. Therefore, the NOAEL at the injection site was not established.

No toxicologic effects related to weekly iv administration (4 doses) of unlabeled PSMA-617 were observed in Sprague Dawley rats at the doses of 0.04, 0.16, or 0.40 mg/kg. The NOAEL for this study in rats was considered the highest tested dose (0.40 mg/kg), which corresponds to a dose approximately 15-fold higher than the maximum human PSMA-617 ligand dose (275 µg) based on BSA scaling.

Safety pharmacology studies indicated no effects of the test solution on CNS or respiratory functions in the rat when administered as a single iv dose, or on cardiovascular function when administered to minipigs. The margins of exposure at the highest dose levels tested corresponded to doses approximately 70-fold (rat) and 215-fold (minipig) higher than the maximum human PSMA-617 dose (275 µg) based on BSA scaling. Further, there was no inhibition of hERG tail current when the ^{175}Lu-PSMA-617 test solution was evaluated in vitro at concentrations up to approximately 1000-fold higher than the estimated PSMA-617 C_{max}.

Unlabeled PSMA-617 was not genotoxic in the *in vitro* bacteria reverse mutation assay (Ames test). It should be noted that the human drug product ^{177}Lu-PSMA-617 is radioactive, and radiation is considered carcinogenic and mutagenic.

The safety of unlabeled PSMA-617 as well a test solution containing non-radioactive ^{175}Lu-PSMA-617 was well characterized in the nonclinical studies, and the nonclinical data support the clinical use of ^{177}Lu-PSMA-617 in the proposed patient population. The details are presented in the [Nonclinical Overview-Section 5].

1.1.2.3 Other sources of safety data

No other safety data apart from the study PSMA-617-01, and the study PSMA-617-02 contributed to the overall safety assessment for this submission.

1.1.2.4 Pooled safety data analyses

Safety analyses are based on the individual results from the pivotal controlled randomized Phase III study PSMA-617-01 (VISION); and the supportive Phase II study PSMA-617-02 (RESIST-PC). PSMA-617-01 was Endocyte-sponsored from the outset, while PSMA-617-02 was investigator-sponsored for most of its conduct and terminated early before full accrual.

No pooled safety data are presented in this submission due to the differences in the studies, considering their origins, designs (with and without comparator), target patient population, safety collection processes (e.g. AE severity grading), treatment regimen and duration (with or without BSC/BSoC).

1.1.2.5 Additional Statistical analyses not included in the individual study reports

In addition to the individual studies, the following subgroup safety analysis were performed in PSMA-617-01. See Section 5 for details on safety analysis in special groups.

- by Region (North America vs. Europe). North America includes sites from United States, United States Satellite site and Canada. Europe includes sites from Belgium, France, United Kingdom, Denmark, Sweden and Netherlands. Germany is excluded since they recruited only patients for the non-randomized sub-study and did not contribute patients to the randomized part of the trial
- by concurrent use of NAADs as part of BSC/BSoC treatment at any time (yes vs. no)
- by concurrent use of external beam radiation therapy as part of BSC/BSoC treatment at any time (yes vs. no)
- by concurrent use of bone sparing agents as part of BSC/BSoC treatment at any time (yes vs. no)

- by age (<65; ≥65-<75; ≥75 years)
- by baseline eGFR level (normal vs. mild impairment vs. moderate impairment vs. severe impairment)
- by baseline proteinuria (≥100mg/dl, "Positive", "2+" , "3+" and "4+" vs. all others)
- by baseline eGFR and proteinuria (eGFR <90 mL/min and proteinuria (≥100mg/dl , "Positive", "2+" ,"3+" and "4+") vs. eGFR ≥ 90 mL/min or proteinuria not in ((≥100mg/dl, "Positive", "2+" and "3+", "4+")
- by patients with renal impairment based on medical history (yes vs. no)
- by presence of liver metastases at baseline (based on CRF data) (yes vs. no)
- by baseline liver parameters ((ALT or AST >ULN) and BILI > ULN vs. (ALT and AST ≤ULN) or BILI ≤ ULN), and
- by patients with hepatic impairment based on medical history (yes vs. no).

1.2 Overall extent of exposure

Overall, 529 patients from the PSMA-617-01 study provide the main analysis for safety of ^{177}Lu-PSMA-617 (7.4 GBq)+BSC/BSoC.

Overall, 30 patients from the PSMA-617-01 sub-study who received ^{177}Lu-PSMA-617 (7.4 GBq)+BSC/BSoC were assessed for dosimetry, PK, urine metabolites, and ECG only. Data from the patients in the sub-study were not included in the randomized part of the trial.

Overall, 64 patients from the PSMA-617-02 study were treated either with 6.0 GBq (N=23) or 7.4 GBq (N=41) of ^{177}Lu-PSMA-617. In this study patients did not consistently receive BSoC along with ^{177}Lu-PSMA-617; therefore, this study data is being presented separately as supportive evidence of the safety profile of ^{177}Lu-PSMA-617.

The overall extent of ^{177}Lu-PSMA-617 exposure from both the studies is described in the individual CSRs; and the extent of exposure data for the PSMA-617-01 sub-study will be included in a Dosimetry Study Report addendum that will accompany the main study report for PSMA-617-01. See [Study PSMA-617-01-Appendix 16.2.9.4].

1.2.1 Duration of exposure

1.2.1.1 Duration of exposure in PSMA-617-01

See Table 1-2 for an overview of the duration of exposure to randomized treatment for the 2 randomized arms Cycles here refer to the "scheduled visits", which were every 6 weeks for the first 6 cycles and then every 12 weeks after Cycle 6.

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. See [Study PSMA-617-01-Section 10.5.1.2] and [Study PSMA-617-01-Table 14.1.4].

See [SCS Appendix 1-Table 71] for exposure-adjusted incidence rate of AEs by preferred term and severity (FAS Safety Analysis Set).

Table 1-2 Duration of exposure to randomized treatment (FAS Safety Analysis Set) in the PSMA-617-01 study

	^{177}Lu-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

Source: [Study PSMA-617-01-Table 14.3.5.2.1]

1.2.1.1.1 Duration of exposure to ^{177}Lu-PSMA-617:

Duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles:

In ^{177}Lu-PSMA-617+BSC/BSoC arm 46.5% of the patients had received 6 cycles of ^{177}Lu-PSMA-617, the maximum number of cycles planned per protocol, and 67.7% patients received at least 4 cycles, the minimum recommended per protocol. The mean (SD) dose intensity 5.5 (1.2) GBq/month, and mean (SD) cumulative dose 33.4 (12.8) GBq are considered safe doses. See [Study PSMA-617-01–Section 9.4.5.2]. Delaying of cycles due to AEs was relatively infrequent (7.6%).

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

One of the 2 patients died due to due to metastases to central nervous system; the Investigator reported metastases to central nervous system as not related to ^{177}Lu-PSMA-617 or BSC/BSoC treatment [Study PSMA-617-01-Listing 16.2.7.4]. The other patient died due to bone marrow failure. The patient had received only 1 dose of ^{177}Lu-PSMA-617. 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. The Investigator reported the events (anaemia, thrombocytopenia, bone marrow failure) as possibly related to the treatment. Individual narratives for all serious TEAEs are provided in Individual narratives for all serious TEAEs are provided in [Study PSMA-617-01-Section 14.3.3].

See [Study PSMA-617-01–Listing 16.2.1.2], [Study PSMA-617-01-Listing 16.2.5.1.1] and [Study PSMA-617-01–Listing 16.2.5.1.2].

See Table 1-3 for an overview of duration of exposure to ^{177}Lu-PSMA-617 and summary of cycles for patients randomized to ^{177}Lu-PSMA-617+BSC/BSoC only arm in the PSMA-617-01 study.

Table 1-3 Duration of ^{177}Lu-PSMA-617 exposure in PSMA-617-01 and summary of cycles (FAS Safety Analysis Set)

	^{177}Lu-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
Minimum 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 ^{177}Lu-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)	
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]

Mode of administration:

In PSMA-617-01, the dose was to be administered slowly by intravenous route, with a saline flush both before and after administration of the dose. The actual method of administration selected to deliver the dose intravenously to the patient was recorded in the CRF. Syringe with or without a pump was the predominant method selected for administration of ^{177}Lu-PSMA-617 in PSMA-617-01 with 1784 total administrations. The other 2 intravenous methods of administration, gravity method and vial with pump, were selected much less frequently with 229 and 344 total administrations, respectively. This administration data collected from PSMA-617-01 supports the inclusion of 3 intravenous methods of administration considered appropriate and safe for administration of the commercial drug product: intravenous injection using a disposable syringe fitted with a syringe shield (with or without a syringe pump) or intravenous infusion using the gravity method (with or without an infusion pump) or using the vial with a peristaltic infusion pump. Instructions for each of these intravenous methods of administration are proposed in the labeling based on experience in PSMA-617-01 and with other RLT such as Lutathera™. See [SCS Appendix 1-Table 70] for the number of ^{177}Lu-PSMA-617 injections by methods of administration in the FAS Safety Analysis Set population.

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

See Table 1-4 for dose reductions and interruptions of ^{177}Lu-PSMA-617 treatment during the actual treatment administration. Note, that TEAEs leading to delays in schedule are being described in a different section. See [Study PSMA-617-01-Section 12.2.4].

Overall, only 16 (3.0%) patients had at least 1 dose interrupted, and none of the interruptions were due to TEAEs. Overall, 30 (5.7%) patients had at least 1 dose reduced (due to TEAEs). Note that per protocol only 1 dose reduction was allowed.

See [Study PSMA-617-01-Listing 16.2.5.1.1] for dose administered per patient. The incidences of dose reductions were similar for all cycles, with no apparent increase with additional cycles of treatment.

Table 1-4 Dose reductions and dose interruptions of ^{177}Lu-PSMA-617 in PSMA-617-01 (FAS Safety Analysis Set)

		^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)
Overall	Number of patients with at least one dose interrupted	16 (3.0)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	14 (2.6)
	Other	2 (0.4)
	Number of patients with at least one dose reduced (due to AE)	30 (5.7)
Cycle 1	Number of patients with at least one dose interrupted	0

		^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	0
	Other	0
	Number of patients with at least one dose reduced (due to AE)	0
Cycle 2	Number of patients with at least one dose interrupted	8 (1.5)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	8 (1.5)
	Other	0
	Number of patients with at least one dose reduced (due to AE)	10 (1.9)
Cycle 3	Number of patients with at least one dose interrupted	0
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	0
	Other	0
	Number of patients with at least one dose reduced (due to AE)	8 (1.5)
Cycle 4	Number of patients with at least one dose interrupted	5 (0.9)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	4 (0.8)
	Other	1 (0.2)
	Number of patients with at least one dose reduced (due to AE)	6 (1.1)
Cycle 5	Number of patients with at least one dose interrupted	3 (0.6)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	2 (0.4)
	Other	1 (0.2)
	Number of patients with at least one dose reduced (due to AE)	5 (0.9)
Cycle 6	Number of patients with at least one dose interrupted	4 (0.8)
	Number of patients with at least one dose interrupted by reason	
	Adverse event	0
	Administration issue	3 (0.6)
	Other	1 (0.2)
	Number of patients with at least one dose reduced (due to AE)	3 (0.6)

Source: [Study PSMA-617-01-Table 14.3.5.3.1]
^{177}Lu-PSMA-617 cycles are once every 6 weeks for a maximum of 6 cycles

1.2.1.1.2 Duration of Exposure to BSC/BSoC and by NAAD as part of assigned BSC/BSoC

See Table 1-5 for duration of exposure to BSC/BSoC.

See [Study PSMA-617-01-Table 14.3.5.2.1.2] for further details on concomitant therapy indicated as BSC/BSoC. Also see [Study PSMA-617-01-Section 10.4.4.4].

Table 1-5 Duration of exposure to BSC/BSoC in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC N=529	BSC/BSoC only N=205
Duration of exposure to BSC/BSoC (months)		
Mean (SD)	8.8 (5.8)	3.5 (3.9)
Median	7.6	2.1
Min-Max	0.3-31.3	0.0-26.0

Source: [Study PSMA-617-01-Table 14.3.5.2.1.2]

The proportion of patients who received NAADs as BSC/BSoC was lower (52.6% patients vs. 67.8% patients) in ^{177}Lu-PSMA-617+BSC/BSoC arm. This might be related to a higher inclination of some Investigators to prescribe the protocol-permitted treatments, NAADs, to the patients who were randomized to receive BSC/BSoC only, as BSC/BSoC could be modified over time as needed.

See Table 1-6 for type and duration of exposure to NAADs indicated as BSC/BSoC. Also see [SCS Appendix 1-Table 70] for the number of ^{177}Lu-PSMA-617 administrations by methods in the FAS Safety Analysis Set population in the PSMA-617-01 main study.

Table 1-6 Type and duration of exposure to NAADs indicated as BSC/BSoC in the PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC N=529	BSC/BSoC only N=205
Number of patients with at least one NAAD indicated as study BSC/BSoC, n (%) [1]	278 (52.6)	139 (67.8)
Type of NAAD, n (%)		
ENZALUTAMIDE	157 (29.7)	87 (42.4)
ABIRATERONE	132 (25.0)	72 (35.1)
APALUTAMIDE	10 (1.9)	1 (0.5)
DAROLUTAMIDE	2 (0.4)	1 (0.5)
Duration of exposure to NAAD as study BSC/BSoC (months)		
n	278	139
Mean (SD)	8.3 (6.2)	3.6 (4.2)
Median	6.6	2.1
Min-Max	0.0-30.9	0.1-26.0

1 NAADs indicated as BSC/BSoC are all NAAD medications indicated as BSC/BSoC (per Endocyte pre-specified list) starting on or after the start of randomized treatment or starting prior to and continuing after the start of randomized treatment but not more than 30 days after end of randomized treatment.
Every patient is counted a single time for each type of NAAD.
Source: [Study PSMA-617-01-Table 14.3.5.6.7]

1.2.1.2 Duration of exposure in PSMA-617-02

Exposure to all treatment cycles were similar between both treatment arms.

The overall duration of study treatment for the mean (SD) number of patients was 3.60 (2.13) months: 3.49 (2.37) months in the 6.0 GBq ^{177}Lu-PSMA-617 arm; and 3.66 (2.01) months in the 7.4 GBq ^{177}Lu-PSMA-617 arm.

There was good compliance in both the groups. Patients received their intended dose for each cycle as per the protocol. Based on dose and relative dose percentage as expected, cumulative dose for the 6.0 GBq group had a mean dose of 16.9 GBq, which was lower compared with the dose for the 7.4 GBq group, which had a mean dose of 21.4 GBq. See [Study PSMA-617-02-Section 12.1.1].

See [Study PSMA-617-02 -Table 14.3.3.1.1] and [Study PSMA-617-02-Table 14.3.3.2.1] for further details on the randomized treatment exposure and summary of cycles.

1.2.2 Patient disposition

1.2.2.1 Patient disposition in PSMA-617-01

In the PSMA-617-01 study, an imbalance was observed in the patient disposition across the 2 treatment arms, mainly due to withdrawal of consent from treatment from the BSC/BSoC only arm. No notable differences were observed for any other parameters.

Overall 831 patients were randomized: 551 patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm; and 280 patients in the BSC/BSoC only arm. Of these, 734/831 (88.3%) patients received at least 1 dose of treatment: 529 patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 205 patients in the BSC/BSoC arm.

Eighteen (3.3% patients) in the ^{177}Lu-PSMA-617+BSC/BSoC arm; and 79 (28.2%) patients in the BSC/BSoC only arm did not receive any treatment at all.

In the PSMA-617-01 study, the patient disposition was similar between the 2 randomized treatment arms in both the FAS and FAS Safety Analysis Set populations. See Figure 1-1, and Table1-7. Also see [Study PSMA-617-01–Table 14.1.4].

^{177}Lu-PSMA-617+BSC/BSoC

Overall, 533/551 (96.7%) patients randomized to ^{177}Lu-PSMA-617+BSC/BSoC received at least 1 dose of treatment: 529 (96.0%) patients received ^{177}Lu-PSMA-617; 4 (0.7%) patients in this arm received only BSC/BSoC (and are included in the BSC/BSoC only arm in the FAS safety analysis set); and 18 (3.3%) patients did not receive any treatment. See [Study PSMA-617-01-Table 14.1.4] for further details.

Discontinuation after receiving treatment: The main reasons to discontinue ^{177}Lu-PSMA-617 treatment (52.7% patients) were progressive disease (24.0% patients); AEs (10.2% patients); and no longer clinically benefiting (6.8% patients). All other reasons were <5.0%: withdrew consent for treatment; investigator decision; death; patient requires care not allowed in the study; other; and subject lost to follow-up.

BSC/BSoC only arm

Overall, 201/280 patients (71.8%) patients randomized to BSC/BSoC only arm received at least 1 dose of treatment; and 4 (0.7%) patients from the ^{177}Lu-PSMA-617+BSC/BSoC who received only BSC/BSoC treatment were included in the BSC/BSoC only arm for the saftey analysis. See [Study PSMA-617-01-Table 14.1.4] for further details.

Discontinuation after receiving treatment: Majority of the patients in the BSC/BSoC only arm (97.6%) patients discontinued treatment. The main reasons to discontinue treatment were: progressive disease (35.6% patients); no longer clinically benefiting (24.4% patients); withdrew consent for treatment (18.0% patients); and Investigator decision and patient requires care not allowed in study (5.4% patients each). All other reasons were <5.0%: AEs; death; other; subject non-compliance; subject lost to follow-up; and protocol deviation. See Table 1-7.

Treatment arm comparison based on treatment discontinuation

The reasons for treatment discontinuation were generally similar between both treatment arms in the FAS safety analysis set population (^{177}Lu-PSMA-617+BSC/BSoC vs BSC/BSoC only), with the exception of progressive disease (24.0% patients vs. 35.6% patients); AEs (10.2% patients vs. 2.0% patients); no longer clinically benefiting (6.8% patients vs. 24.4% patients); and withdrew consent for treatment (4.3% patients vs. 18.0% patients). See Section 1.2.1 for exposure related information.

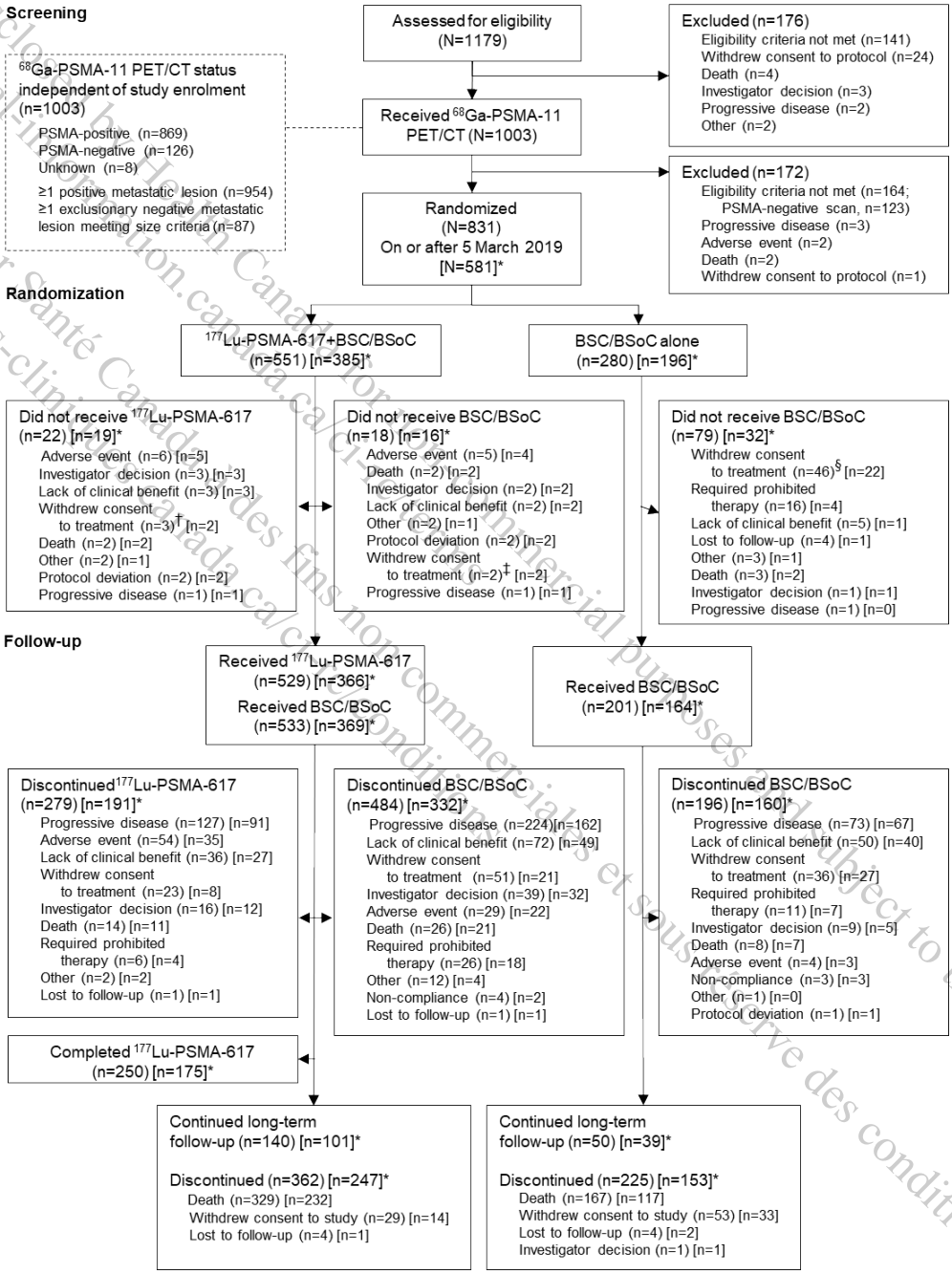
Discontinuation from Study

At data cutoff (27-Jan-2021), 64.3% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 76.1% patients in the BSC/BSoC only arm had discontinued from the study. The main reasons for study discontinuation (^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only) were death (58.4% patients vs. 64.4% patients), and withdrew consent for participation in study (5.1% patients vs. 10.7% patients). All other reasons were <5.0%: subject lost to follow-up; and Investigator decision.

See Table 1-7 for patient disposition – end of treatment and end of study status in PSMA-617-01 (FAS Safety Analysis Set).

See [Study PSMA-617-01-Table 14.1.4] and [Study PSMA-617-01-Table 14.1.4.2] for further details on patient disposition in the FAS population.

Figure 1-1 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].

Table 1-7 Patient disposition – End of Treatment and End of Study Status in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)	Overall N=734 n (%)
Patients treated	529 (100)	205 (100)	734 (100)
Patients still on treatment [1]	49 (9.3)	5 (2.4)	54 (7.4)
Patients who completed ^{177}Lu-PSMA-617	250 (47.3)		
Patients who discontinued from all study treatments	**480 (90.7)**	**200 (97.6)**	**680 (92.6)**
Patients who discontinued from ^{177}Lu-PSMA-617	**279 (52.7)**		
Reason for discontinuation from ^{177}Lu-PSMA-617			
Progressive disease	127 (24.0)		
Adverse event	54 (10.2)		
No longer clinically benefiting	36 (6.8)		
Withdrew consent (treatment)	23 (4.3)		
Investigator decision	16 (3.0)		
Death	14 (2.6)		
Patient requires care not allowed in the study	6 (1.1)		
Other	2 (0.4)		
Subject lost to follow-up	1 (0.2)		
Patients who discontinued from BSC/BSoC	**480 (90.7)**	**200 (97.6)**	**680 (92.6)**
Reason for discontinuation from BSC/BSoC			
Progressive disease	224 (42.3)	73 (35.6)	297 (40.5)
No longer clinically benefiting	72 (13.6)	50 (24.4)	122 (16.6)
Withdrew consent (treatment)	50 (9.5)	37 (18.0)	87 (11.9)
Investigator decision	37 (7.0)	11 (5.4)	48 (6.5)
Adverse event	29 (5.5)	4 (2.0)	33 (4.5)
Patient requires care not allowed in the study	26 (4.9)	11 (5.4)	37 (5.0)
Death	25 (4.7)	9 (4.4)	34 (4.6)
Other	12 (2.3)	1 (0.5)	13 (1.8)
Subject non-compliance	4 (0.8)	3 (1.5)	7 (1.0)
Subject lost to follow-up	1 (0.2)	0	1 (0.1)
Protocol deviation	0	1 (0.5)	1 (0.1)
Patients who discontinued from study	**340 (64.3)**	**156 (76.1)**	**496 (67.6)**
Reason for discontinuation from study			
Death	309 (58.4)	132 (64.4)	441 (60.1)
Withdrew consent (protocol)	27 (5.1)	22 (10.7)	49 (6.7)
Subject lost to follow-up	4 (0.8)	1 (0.5)	5 (0.7)
Investigator decision	0	1 (0.5)	1 (0.1)

[1] Patients still on treatment at the time of the data cut-off date 27-JAN-2021
Source: [SCS Appendix 1-Table 1]

1.2.2.2 Patient disposition in PSMA-617-02

In the PSMA-617-02 study, there was an imbalance in the patient disposition across the 2 treatment arms, i.e., of the 71 patients enrolled and randomized (ITT population), 28 patients were assigned to the 6.0 GBq dose arm, and 43 patients were assigned to the 7.4 GBq dose arm. This imbalance can be attributed to the early termination of the study. Seven patients (9.9%)

were randomized but not treated; hence the SAS had 64 patients: 23 patients in the 6.0 GBq dose arm, and 41 patients in the the 7.4 GBq.

See [Study PSMA-617-02-Table 14.1.2], [Study PSMA-617-02-Listing 16.2.1.2] and [Study PSMA-617-02-Listing 16.2.1.1] for further details on patient disposition and reasons for treatment discontinuations in the PSMA-617-02 study.

1.3 Demographic and other characteristics of study population

1.3.1 Inclusion and exclusion criteria

1.3.1.1 Inclusion and exclusion criteria in PSMA-617-01

Adult male patients were qualified for enrollment if they met the following key criteria at screening:

- Had a positive ^{68}Ga-PSMA-11 PET/CT scan, and eligible as determined by the Endocyte's central reader.
- Had a histological, pathological, and/or cytological confirmation of PC.
- Had received at least 1 NAAD.
- Had documented progressive mCRPC based on at least 1 of the PCWG3 criteria for serum/plasma PSA progression, soft-tissue progression, or progression of bone disease.
- Were previously treated with at least 1, but no more than 2 prior taxane regimens (a taxane regimen defined as a minimum exposure of 2 cycles of a taxane).
- Had an ECOG performance status of 0 to 2.
- Had ≥ 1 metastatic lesion that was present on baseline CT, MRI, or bone scan imaging (obtained less than or equal to 28 days prior to beginning study therapy).
- Had adequate bone marrow reserve, hepatic and renal function.

Patients were excluded if they were exposed to any previous PSMA-targeted RLT, radioisotopes or hemi-body irradiation within 6 months of randomization, or any investigational agents or systemic anti-cancer therapy within 28 days prior to the date of randomization, or had known hypersensitivity to the components of the study therapy or its analogs. Patients were also not allowed to receive other concurrent cytotoxic chemotherapy, immunotherapy, other systemic radioisotopes (e.g., Ra-223), hemi-body irradiation, or investigational therapy.

See [Study PSMA-617-01 Appendix 16.1.1 Protocol–Section 4.1] for all the inclusion criteria; and [Study PSMA-617-01 Appendix 16.1.1 Protocol–Section 4.2] for all the exclusion criteria in the PSMA-617-01 study.

1.3.1.2 Inclusion and exclusion criteria in PSMA-617-02

All patients in PSMA-617-02 had to have progressive mCRPC with confirmed testosterone level ≤ 50 ng/ml under prior androgen deprivation therapy, and positive ^{68}Ga-PSMA-11 PET/CT, or diagnostic ^{177}Lu-PSMA-617 scintigraphy, or any equivalent PSMA-directed imaging. Patients were required to have and ECOG score of 0-2, and sufficient bone marrow capacity and to be previously exposed to either enzalutamide or abiraterone.

Patients were excluded if they had received their last myelosuppressive therapy (including docetaxel, cabazitaxel, ^{223}Ra, ^{153}Sm) within 6 weeks of study entry; had a GFR < 40 mL/min;

had serum creatinine > 1.5xULN; had AST or ALT > 5xULN; had a urinary tract obstruction or marked hydronephrosis; or there was a diffuse bone marrow involvement confirmed by super-scans.

See [Study PSMA-617-02 Appendix 16.1.1 Protocol-Section 4.2] for all the inclusion criteria; and [Study PSMA-617-02 Appendix 16.1.1 Protocol-Section 4.3] for all the exclusion criteria in the PSMA-617-02 study.

1.3.2 Demographics

1.3.2.1 Demographics in PSMA-617-01

In the PSMA-617-01 study, the demographics and baseline characteristics were balanced between the 2 randomized treatment arms in both the FAS and FAS Safety Analysis Set populations. The baseline characteristics were representative of the mCRPC population.

See Table 1-8 and [Study PSMA-617-01-Table 14.1.7.3] for the demographic and baseline characteristics in the FAS Safety Analysis Set; and see [Study PSMA-617-01-Table 14.1.7.1] for the FAS population.

Table 1-8 Demographics and other baseline characteristics in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC N=529	BSC/BSoC only N=205	Overall N=734
Age (years)			
n	529	205	734
Mean (SD)	69.6 (7.4)	70.5 (7.8)	69.8 (7.5)
Median	70.0	71.0	70.0
Min-Max	48-94	40-89	40-94
Age (categorized), n (%)			
< 65 years	142 (26.8)	42 (20.5)	184 (25.1)
≥ 65 years	387 (73.2)	163 (79.5)	550 (74.9)
≥ 65-84 years	379 (71.6)	157 (76.6)	536 (73.0)
≥ 85 years	8 (1.5)	6 (2.9)	14 (1.9)
Race, n (%)			
White	465 (87.9)	173 (84.4)	638 (86.9)
Black or African American	34 (6.4)	19 (9.3)	53 (7.2)
Asian	9 (1.7)	8 (3.9)	17 (2.3)
Other [1]	2 (0.4)	0	2 (0.3)
Missing	19 (3.6)	5 (2.4)	24 (3.3)
Ethnicity, n (%)			
Hispanic or Latino	11 (2.1)	2 (1.0)	13 (1.8)
Not Hispanic or Latino	457 (86.4)	171 (83.4)	628 (85.6)
Not reported	61 (11.5)	32 (15.6)	93 (12.7)
Weight (kg)			
n	514	198	712
Mean (SD)	88.20 (17.3)	87.49 (16.2)	88.00 (17.0)
Median	85.81	84.86	85.60

	^{177}Lu-PSMA-617 +BSC/BSoC N=529	BSC/BSoC only N=205	Overall N=734
Min-Max	54.0-160.0	52.3-147.0	52.3-160.0
Height (cm)			
n	501	193	694
Mean (SD)	176.3 (7.3)	176.2 (7.5)	176.3 (7.4)
Median	176.0	176.0	176.0
Min-Max	152-206	155-194	152-206
Body mass index (kg/m^2)			
n	496	192	688
Mean (SD)	28.40 (5.1)	28.07 (4.8)	28.31 (5.0)
Median	27.77	27.39	27.71
Min-Max	17.0-48.4	20.3-44.6	17.0-48.4
ECOG performance status, n (%) [2]			
0-1	494 (93.4)	189 (92.2)	683 (93.1)
2	35 (6.6)	16 (7.8)	51 (6.9)

[1] Other includes Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native and more than one race reported.
[2] ECOG performance status was not collected at the time of screening and was only captured as the categories 0-1 vs. 2 on the enrollment CRF page.
Source: [PSMA-617-01-Table 14.1.7.3]

1.3.2.2 Demographics in PSMA-617-02

In the PSMA-617-02 study, the demographics and baseline characteristics were representative of the mCRPC population, and were generally balanced between the 2 treatment arms.

See [Study PSMA-617-02-Table 14.1.4.1] for further details on demographics at baseline for the PSMA-617-02 study.

1.3.3 Disease characteristics

1.3.3.1 Disease characteristics in PSMA-617-01

The baseline disease characteristics were balanced between the 2 randomized treatment arms in both the FAS and FAS Safety Analysis Set populations.

See Table 1-9 and [Study PSMA-617-01–Table 14.1.8.3] for baseline disease characteristics (FAS Safety Analysis Set); and see [Study PSMA-617-01-Table 14.1.8.1] for baseline disease characteristics (FAS).

Table 1-9 Disease characteristics for all randomized patients at baseline (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+ BSC/BSoC N=529	BSC/BSoC only N=205	Overall N=734
Time since initial cancer diagnosis (years)			
n	529	205	734
Mean (SD)	8.37 (5.5)	8.70 (6.0)	8.46 (5.6)
Median	7.42	6.85	7.26

	^{177}Lu-PSMA-617+ BSC/BSoC N=529	BSC/BSoC only N=205	Overall N=734
Min-Max	0.9-25.2	0.7-28.9	0.7-28.9
Initial histopathological classification, n (%)			
Adenocarcinoma	477 (90.2)	193 (94.1)	670 (91.3)
Neuroendocrine	1 (0.2)	0	1 (0.1)
Unknown	45 (8.5)	11 (5.4)	56 (7.6)
Other	6 (1.1)	1 (0.5)	7 (1.0)
Initial histopathological grade, n (%)			
grade 1	10 (1.9)	2 (1.0)	12 (1.6)
grade 2	7 (1.3)	5 (2.4)	12 (1.6)
grade 3	37 (7.0)	9 (4.4)	46 (6.3)
grade 3-4	14 (2.7)	6 (2.9)	20 (2.7)
grade 4	49 (9.3)	25 (12.2)	74 (10.1)
grade 5	62 (11.8)	28 (13.7)	90 (12.3)
Unknown	347 (66.0)	130 (63.4)	477 (65.3)
Initial Gleason score, categorized, n (%)			
2-3	4 (0.8)	0	4 (0.5)
4-7	175 (33.1)	60 (29.3)	235 (32.0)
8-10	313 (59.2)	125 (61.0)	438 (59.7)
Unknown	37 (7.0)	20 (9.8)	57 (7.8)
Staging at initial diagnosis, n (%)			
I	8 (1.5)	3 (1.5)	11 (1.5)
IA	0	1 (0.5)	1 (0.1)
IB	3 (0.6)	3 (1.5)	6 (0.8)
II	25 (4.8)	7 (3.4)	32 (4.4)
IIA	19 (3.6)	6 (2.9)	25 (3.4)
IIB	22 (4.2)	8 (3.9)	30 (4.1)
III	23 (4.4)	7 (3.4)	30 (4.1)
IIIA	22 (4.2)	4 (2.0)	26 (3.6)
IIIB	38 (7.2)	9 (4.4)	47 (6.4)
IIIC	2 (0.4)	3 (1.5)	5 (0.7)
IV	68 (12.9)	39 (19.1)	107 (14.7)
IVA	10 (1.9)	4 (2.0)	14 (1.9)
IVB	20 (3.8)	9 (4.4)	29 (4.0)
Unknown	266 (50.6)	101 (49.5)	367 (50.3)
Baseline target lesions, n (%)			
Yes	265 (50.1)	103 (50.2)	368 (50.1)
No	264 (49.9)	102 (49.8)	366 (49.9)
Baseline non-target lesions, n (%)			
Yes	409 (77.3)	150 (73.2)	559 (76.2)
No	120 (22.7)	55 (26.8)	175 (23.8)
Total sum of target lesion diameters (mm)			
n	265	103	368
Mean (SD)	58.3 (45.8)	57.1 (44.6)	57.9 (45.4)
Median	45.0	44.0	44.9
Min-Max	11-351	10-249	10-351

	^{177}Lu-PSMA-617+ BSC/BSoC N=529	BSC/BSoC only N=205	Overall N=734
Site of disease (target and non-target lesions), n (%) [1]			
Lung			
Yes	44 (8.3)	20 (9.8)	64 (8.7)
No	485 (91.7)	185 (90.2)	670 (91.3)
Liver			
Yes	58 (11.0)	23 (11.2)	81 (11.0)
No	471 (89.0)	182 (88.8)	653 (89.0)
Lymph node			
Yes	261 (49.3)	108 (52.7)	369 (50.3)
No	268 (50.7)	97 (47.3)	365 (49.7)
Bone			
Yes	482 (91.1)	187 (91.2)	669 (91.1)
No	47 (8.9)	18 (8.8)	65 (8.9)
Baseline PSA doubling time (months) [2]			
n	257	96	353
Mean (SD)	3.17 (5.4)	4.53 (10.3)	3.54 (7.1)
Median	2.38	2.70	2.43
Min-Max	0.0-74.4	0.0-93.1	0.0-93.1
Baseline PSA doubling time (categorized), n (%)			
Stable, non-increasing or decreasing	6 (2.3)	5 (5.2)	11 (3.1)
≤ 6 months	238 (92.6)	82 (85.4)	320 (90.7)
> 6 months	13 (5.1)	9 (9.4)	22 (6.2)
Baseline PSA (ng/mL)			
n	529	205	734
Mean (SD)	257.1 (580.2)	428.6 (1041.6)	305.0 (741.9)
Median	69.1	83.3	75.5
Min-Max	0-6360	0-8995	0-8995
Baseline ALP (IU/L)			
n	525	204	729
Mean (SD)	142.1 (128.7)	142.7 (155.5)	142.2 (136.6)
Median	102.0	94.5	99.0
Min-Max	26-952	32-1355	26-1355
Baseline LDH (IU/L)			
n	528	205	733
Mean	268.2 (153.6)	302.9 (281.9)	277.9 (198.4)
Median	219.0	228.0	222.0
Min-Max	88-1508	105-2693	88-2693

[1] Bone site of disease was based on data collected on target and/or non-target lesion or bone scan assessments.
[2] Baseline PSA doubling time was derived for each patient as the natural log 2 divided by the sum of the fixed and random slopes of the random coefficient linear model between natural log of PSA and time of PSA measurement (in months). Patients with at least 3 PSA values prior to and at the time of screening were included in the model.
Source: [Study PSMA-617-01-Table 14.1.8.3]

1.3.3.2 Disease characteristics in PSMA-617-02

In the PSMA-617-02 study, the baseline disease characteristics were generally balanced between the treatment arms with some minor differences. The study was terminated early and consequently, the number of patients were low; hence, it was not possible to draw any meaningful comparison.

See [Study PSMA-617-02-Table 14.1.5.1] for further details on the disease characteristics at baseline in the PSMA-617-02 study.

1.3.4 Prior anticancer therapy

Overall, prior anticancer therapy for both PSMA-617-01 and PSMA-617-02 studies, was as anticipated for a population of patients with an advanced disease with a relative long time since initial diagnosis. Further details of the prior anticancer therapies for the individual studies are presented in the following sections.

1.3.4.1 Prior and concomitant medications or treatments in PSMA-617-01

1.3.4.1.1 Medical history

Medical history for the FAS and the FAS Safety Analysis Set populations, including past medical conditions/procedures that ended before the time of informed consent, are presented in [Study PSMA-617-01-Table 14.1.9.1] and [Study PSMA-617-01-Table 14.1.9.3], respectively. This medical history was similar in both arms and for both analysis sets.

1.3.4.1.2 Prior anticancer therapy

Overall, prior anticancer therapies were balanced between the 2 randomized treatment arms and as expected in this patient population for both the FAS and FAS Safety Analysis Set populations.

Prior cancer-related surgery:

The cancer-related surgeries were balanced between the 2 treatment arms in both the FAS and FAS Safety Analysis Set populations.

In the FAS Safety Analysis Set population, 96.3% patients had at least 1 PC–related surgery (including biopsies); and 42.2% of patients had undergone therapeutic surgeries.

See [Study PSMA-617-01-Table 14.1.11.1] and [Study PSMA-617-01-Table 14.1.11.3] for the prior cancer-related surgeries in the FAS, and FAS Safety Analysis Set populations, respectively.

Prior cancer-related radiotherapy

The cancel-related radiotherapies were balanced between the 2 treatment arms in both the FAS and the FAS Safety Analysis Set populations.

In the FAS Safety Analysis Set population, a majority of patients (76.4% patients) had at least 1 PC–related radiotherapy. The most frequent site for radiotherapy was the prostate gland (44.8% patients).

See [Study PSMA-617-01-Table 14.1.12.1] and [Study PSMA-617-01-Table 14.1.12.3] for the prior cancer-related radiotherapies in the FAS, and FAS Safety Analysis Set populations, respectively.

Prior cancer-related systemic therapy

The prior cancer-related systemic therapies were balanced between the 2 treatment arms in both the FAS and the FAS Safety Analysis Set populations.

Overall, the mean for cancer-related systemic prior regimens for the patients in FAS Safety Analysis Set was 5.3 (median was 5.0) and the majority of patients (79.3%) had received ≥3 different categories of regimens. The most frequent reasons for cancer-related systemic therapies were therapeutics for 78.1% of the patients and adjuvant therapies for 30.9% of the patients. All patients (100%) in the FAS Safety Analysis Set received prior taxane treatment (1 regimen in 58.9% patients, 2 regimens in 40.2% patients, and more than 2 regimens in 1.0% of patients); and prior NAAD (1 NAAD in 53.3% patients, 2 NAADs in 39.5% patients, and more than 2 NAADs in 7.2% patients).

See [Study PSMA-617-01–Table 14.1.13.1] and [Study PSMA-617-01-Table 14.1.13.3] for prior cancer-related systemic therapies in the FAS, and FAS Safety Analysis Set populations, respectively.

1.3.4.1.3 Concomitant therapy

Concomitant medications

All patients (100%) in the FAS Safety Analysis Set received at least 1 concomitant medication. Concomitant medications were balanced between the 2 treatment arms, with differences that were typically <10% between the ^{177}Lu-PSMA-617+BSC/BSoC arm and the BSC/BSoC only arm, respectively except for:

- Serotonin (5HT3) antagonists: 51.2% patients vs. 18.0% patients (mainly ondansetron: 49.7% vs. 16.6%)
- NAAD: 34.6% patients vs. 48.3% patients (mainly enzalutamide: 29.9% vs. 42.9%)

See [Study PSMA-617-01-Table 14.3.11.1.2.1] for concomitant medications during randomized treatment for the FAS Safety Analysis Set population in the PSMA-617-01 study.

Concurrent radiotherapy

Concurrent radiotherapy incidence and sites were balanced between the 2 treatment arms. Overall, 17.8% patients in the FAS Safety Analysis Set received at least 1 radiotherapy; the most frequent site was the back (6.4% patients). See [Study PSMA-617-01-Table 14.3.10.2] for concurrent radiotherapy during randomized treatment for the FAS Safety Analysis Set population in the PSMA-617-01 study.

Concurrent surgical and therapeutic procedures

Concurrent surgical and therapeutic procedures were balanced between the 2 treatment arms. Overall, 22.1% had a least 1 procedure, including 11.9% patients who had at least 1 investigation (the most frequent was chest X-ray, 1.8% patients); and 15.0% patients who had

at least 1 surgical and medical procedure (the most frequent were nephrostomy and uteral stent insertion, 1.9% patients each). See [Study PSMA-617-01-Table 14.3.9.2.1] for concurrent surgical and therapeutic procedures during randomized treatment for the FAS Safety Analysis Set population in the PSMA-617-01 study.

1.3.4.1.4 Concomitant therapy indicated as BSC/BSoC

All patients (100%) in the FAS Safety Analysis Set received at least 1 concomitant medication indicated as BSC/BSoC. The most frequent medication was gonadotropin releasing hormone analogues, reported in 88.5% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm as compared to 83.9% patients in the BSC/BSoC only arm.

Concomitant medications were balanced between the 2 treatment arms, with differences that were typically <10% between the ^{177}Lu-PSMA-617+BSC/BSoC arm and the BSC/BSoC only arm, respectively, except for:

- Serotonin (5HT3) antagonists: 51.0% patients vs. 17.1% patients (mainly driven by ondansetron: 49.3% vs. 15.6%)
- NAADs: 34.4% patients vs. 47.3% patients (mainly driven by enzalutamide, 29.7% vs. 42.4%)
- NAADs: 33.5% patients versus 46.8% patients (mainly enzalutamide: 29.3% vs. 42.0%).

See [Study PSMA-617-01-Table 14.3.5.6.1] for concomitant medications indicated as BSC/BSoC during randomized treatment for the FAS Safety Analysis Set population in the PSMA-617-01 study.

1.3.4.1.5 Concurrent radiotherapies indicated as BSC/BSoC

Concurrent surgical and therapeutic procedures indicated as BSC/BSoC

Incidences and sites of concurrent radiotherapies were balanced between the 2 treatment arms. Overall, 15.4% patients in the FAS Safety Analysis Set received at least 1 concurrent radiotherapy; the most frequent site for radiotherapy was the back (5.4%). See [Study PSMA-617-01-Table 14.3.5.8.1] for concurrent radiotherapies indicated as BSC/BSoC during randomized treatmnet in the FAS Safety Analysis Set population in the PSMA-617-01 study.

These procedures were relatively infrequent in both arms (4.5% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 2.4% patients in BSC/BSoC only arm).

See [Study PSMA-617-01-Table 14.3.5.7.1] for concurrent surgical and therapeutic procedures indicated as BSC/BSoC during randomized treatment for the FAS Safety Analysis Set population in the PSMA-617-01 study.

1.3.4.2 Prior and concomitant medications or treatments in PSMA-617-02

In Study PSMA-617-02, the prior and concomitant medications or treatments were generally balanced between the treatment arms with some minor differences. The study was terminated early and consequently, the number of patients were low; hence, it was not possible to draw any meaningful comparison.

Prostate cancer treatment history – chemotherapy (ITT population)

Previous chemotherapy treatment history was consistent in the ITT Population between the 2 treatment arms, and was considered balanced without any relevant differences. Fifty-eight (81.7%) patients in the ITT population had at least 1 prior chemotherapy treatment for PC prior to study enrollment; 57 (80.3%) patients had at least 1 prior taxane; 54 (76.1%) patients had docetaxel; and 26 (36.6%) patients had cabazitaxel.

See [Study PSMA-617-02-Table 14.1.6.1].

Details about the last chemotherapy treatment received for PC prior to study enrollment had a lot of missing data; hence, it was not possible to draw any meaningful conclusions: 50 (70.4%) patients in the ITT population received taxane as their last therapy.

See [Study PSMA-617-02-Table 14.1.6.3].

Prostate cancer treatment history – previous other treatment (ITT population)

Overall, 71 (100%) patients in the ITT population had a history of at least 1 other treatment for PC prior to study enrollment, including 67 (94.4%) patients with abiraterone and 55 (77.5%) patients with enzalutamide. These were balanced between the 2 treatment arms.

See [Study PSMA-617-02-Table 14.1.6.4].

Prostate cancer treatment history – radiotherapy (ITT population)

Overall, 52 (73.2%) patients in the ITT population had a history of at least one PC-related radiotherapy prior to study enrollment. A greater number of patients (approximately 10%) in the 7.4 GBq group had radiotherapy in one form or other, as compared with the patients in the 6.0 GBq group; however, the number of cycles per patient did not differ between the 2 treatment arms. It is not expected that this had any impact on the overall interpretation of the safety results or on the safety conclusions.

See [Study PSMA-617-02-Table 14.1.6.5].

1.3.4.2.1 Concurrent therapies and treatments

Overall 2 patients, 1 patient in each dose arm in the ITT population received concurrent radiotherapy. No patients received concurrent chemotherapy. The most frequently administered "other concurrent therapy" for both the treatment arms was hormonal therapy (37, 57.8% patients): 12 (52.2%) patients in the 6.0 GBq arm, and 25 (61.0%) patients in the 7.4 GBq arm. Overall 8 (12.5%) patients received abiraterone concurrent therapy, and 9 (14.1%) patients received enzalutamide concurrent therapy.

See [Study PSMA-617-02-Table 14.3.6.1.1], [Study PSMA-617-02-Table 14.3.6.3.1] and [Study PSMA-617-02-Table 14.3.6.2.1] for further details on the use of prior and concomitant therapies in the PSMA-617-02 study.

Medical history for the ITT Population is presented in [Study PSMA-617-02–Listing 16.2.3.2.1].

2 Adverse events

The safety results from the PSMA-617-01 (FAS Safety Analysis Set) and PSMA-617-02 (SAS) were balanced in terms of nature, frequency and severity of TEAEs, taking into account the differences in trial design, population, exposure etc.

2.1 Analysis of adverse events

See Table 2-1 MedDRA and NCI-CTCAE for PSMA-617-01 and PSMA-617-02 for the dictionaries and grading scales used in each study.

Table 2-1 MedDRA and NCI-CTCAE for PSMA-617-01 and PSMA-617-02

Study	MedDRA version	NCI CTCAE version
PSMA-617-01	23.1	5.0
PSMA-617-02	22.1	4.03 only for SAEs; othe AEs were graded as mild, moderate, or severe

Medical Dictionary for Regulatory Activities (MedDRA)

MedDRA system organ classes (SOC) and preferred terms (PT) were used in the analyses of AEs. Adverse events of special interest (AESI) consisted of 1 or more well-defined safety events which were similar in nature. The search criteria were based upon SMQs or customized MedDRA terms as specified in the electronic case retrieval sheet (eCRS).

Common Terminology Criteria for Adverse Events (CTCAE)

Adverse events and laboratory tests were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE). Different versions of CTCAE were used for AE and laboratory value grading as specified in each individual study protocol. Since there were no pooled analyses nor side-by-side presentations for AEs and laboratory data, the grading as reported by the investigator in the individual studies are presented in this SCS. Of note, in PSMA-617-02, only SAEs were graded using CTCAE. Other AEs were graded as mild, moderate, or severe.

2.1.1 Common adverse events

2.1.1.1 Overview of treatment emergent adverse events in PSMA-617-01

In the Study PSMA-617-01, the treatment-emergent period was defined as the period from the date of initiation of randomized treatment up to 30 days after the date of the last administration of randomized treatment, or the day prior to the initiation of subsequent anticancer treatment, whichever occurred first. Adverse events were subsequently collected in the long-term follow-up as self-reported AEs, recorded only with event term and severity.

2.1.1.1.1 TEAEs during randomized treatment period

In both arms, most patients (98.1% patients in ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 82.9% patients in the BSC/BSoC only arm) had at least 1 TEAE.

The TEAEs were usually more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm for all categories except TEAEs leading to reduction of BSC/BSoC. The differences were more 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). An event was reported as drug-related if it was considered by the investigator to be related to any of the study treatments, whether ^{177}Lu-PSMA-617 or BSC/BSoC.

Notably, the higher incidences of TEAEs for all SOCs in ^{177}Lu-PSMA-617+BSC/BSoC arm might be related in part to the longer duration of exposure and a longer observation period in this arm (see Section 1.2.1.1). See [SCS Appendix1-Table 71] for exposure-adjusted incidence rate of AEs by preferred term and severity (FAS Safety Analysis Set).

The imbalance of drug-related and high grade (≥3) drug-related TEAEs as assessed by the investigator, between the ^{177}Lu-PSMA-617+BSC/BSoC arm versus the BSC/BSoC only arm should 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 the Study Drug by some investigators.

An overview of TEAEs during randomized treatment is presented in Table 2-2. Summaries for different categories of TEAEs are presented in next sections.

Table 2-2 Overview of TEAEs during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	**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 ^{177}Lu-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]

Treatment emergent adverse events by system organ class

In the PSMA-617-01 study, the incidence of TEAEs by SOC (for all SOCs) were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

As a result of the higher discontinuation rate from the BSC/BSoC only arm resulting from disease progression, median exposure to treatment with BSC/BSoC only and ^{177}Lu-PSMA-617+BSC/BSoC differed (see Section 1.2.1.1). This imbalance in the treatment

duration of exposure should be considered when comparing the AE incidence rates between the 2 treatment arms.

The greatestdifferences (≥20%) between the 2 treatment arms (^{177}Lu-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

TEAEs reported during randomized treatment by primary SOC and maximum grade in PSMA-617-01 are presented in Table 2-3.

Table 2-3 TEAEs during randomized treatment regardless of study treatment relationship by primary system organ class in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		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 conditions	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 (incl cysts and polyps)	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]

Treatment emergent adverse events by preferred term and maximum grade

In the PSMA-617-01 study the TEAEs were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm. In both arms, the TEAE reported with the highest incidence was fatigue.

The greatestdifferences (≥10%) in the incidence of TEAEs between the 2 treatment arms (^{177}Lu-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

High grade (grade ≥3) TEAEs: Overall, high grade TEAEs (grade ≥3) were relatively infrequent (<5.0% patients) in both arms, except for the following events which were more frequent in the ^{177}Lu-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.

Similarly, although the TEAEs such as dry mouth, nausea, diarrhea, vomiting and UTI were also more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm, they were usually reported with low severity (≤2); and they only led to permanent discontinuation of ^{177}Lu-PSMA-617 in ≤0.5% of patients. See [Study PSMA-617-01-Section 12.2.3] and [Study PSMA-617-01–Table 14.3.2.13.10] for further details on discontinuations.

Notably, these events of fatigue, dry mouth, nausea, vomiting, diarrhea (except UTI), and events of myelosuppression/hematologic events listed here are expected toxicities associated with ^{177}Lu-PSMA-617 treatment. Also, to note, spinal cord compression was observed with a lower frequency in the ^{177}Lu-PSMA-617+BSC/BSoC arm (1.3% patients vs. 5.4% patients in the BSC/BSoC arm).

Frequent TEAEs reported during randomized treatment in at least 5% of the patients in either arm by PT and maximum grade in PSMA-617-01 are presented in Table 2-4.

See [Study PSMA-617-01–Table 14.3.2.13.2] for further details.

Table 2-4 TEAEs during randomized treatment (in at least 5% of patients) regardless of study treatment relationship by preferred term and maximum grade in PSMA-617-01(FAS Safety Analysis Set)

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

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

Drug-related TEAEs during randomized treatment

In the PSMA-617-01 study, the incidence of drug-related TEAEs as assessed by the Investigator were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm as compared to the BSC/BSoC only arm (85.3% patients vs. 28.8% patients). All the drug-related TEAEs in the BSC/BSoC only arm were reported in less than 10% patients each.

The most frequently reported drug-related TEAEs (≥20%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm were: dry mouth (35.9% patients), fatigue (31.2% patients), nausea (28.0% patients), and anemia (25.5% patients).

Drug-related high grade (≥3) TEAEs were more frequently reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The drug-related high grade (≥3) TEAEs that were reported with the highest incidence were anemia (9.6% patients); thrombocytopenia and lymphopenia (6.8% patients each). All other drug-related high grade (≥3) TEAEs were reported in less than 5.0% of patients each.

The results are as expected in ^{177}Lu-PSMA-617 therapy and these events are known toxicities related to the ^{177}Lu-PSMA-617 treatment.

Frequent TEAEs reported during randomized treatment in at least 5% of the patients in either arm that were suspected to be related to the study drug by the Investigator are presented in Table 2-5. See [Study PSMA-617-01–Table 14.3.2.13.4] for further details.

Table 2-5 TEAEs during randomized treatment (in at least 5% of patients) with suspected relationship by preferred term and maximum grade in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**	**All grades n (%)**	**Grade ≥ 3 n (%)**
Number of patients with at least one event	451 (85.3)	150 (28.4)	59 (28.8)	8 (3.9)
Dry mouth	190 (35.9)	0	0	0
Fatigue	165 (31.2)	21 (4.0)	14 (6.8)	0
Nausea	148 (28.0)	5 (0.9)	8 (3.9)	0
Anaemia	135 (25.5)	51 (9.6)	6 (2.9)	1 (0.5)
Thrombocytopenia	83 (15.7)	36 (6.8)	0	0
Decreased appetite	68 (12.9)	6 (1.1)	6 (2.9)	0
Vomiting	63 (11.9)	3 (0.6)	3 (1.5)	0
Lymphopenia	61 (11.5)	36 (6.8)	2 (1.0)	0
Diarrhoea	58 (11.0)	3 (0.6)	0	0
Leukopenia	58 (11.0)	12 (2.3)	3 (1.5)	0
Constipation	45 (8.5)	2 (0.4)	1 (0.5)	0
Neutropenia	43 (8.1)	17 (3.2)	2 (1.0)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.4]

2.1.1.1.2 Long-term follow-up

In the PSMA-617-01 study, long-term follow-up safety data was planned to be collected after the end-of-study visit for a duration of 24 months or until 508 deaths (whichever occurred first). During long-term follow-up, patients were to be contacted every 3 months.

Contact with the patient in the long-term follow-up was typically remote, and the AEs were self-reported and recorded only with event term and severity. As in this period the patients could have been receiving any form of treatment, data for which was not possible to be collected in a structured way, these long-term follow-up data from the PSMA-617-01 study only allow for a limited interpretation.

Overview of AEs during long-term follow-up

The incidence of AEs and high grade AEs (≥3) were similar for both the groups of patients, ie, the incidence of TEAEs overall were similar irrespective of whether the patient had previously been treated in the ^{177}Lu-PSMA-617+BSC/BSoC arm or in the BSC/BSoC only arm during the randomized treatment period.

See Table 2-6 for an overview of AEs during the long-term follow-up in the PSMA-617-01.

Table 2-6 TEAEs during long-term follow-up in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
AE	123 (23.3)	53 (25.9)
grade 3/4/5 AE	61 (11.5)	29 (14.1)
Fatal AE	7 (1.3)	7 (3.4)

Source: [Study PSMA-617-01-Table 14.3.3.1]

Analysis of AEs during long-term follow-up by SOCs and PTs

The incidences of AEs by SOC were similar (≤10% differences) for those patients who had previously received ^{177}Lu-PSMA-617+BSC/BSoC as compared to those who had previously received BSC/BSoC only. The most frequently reported AEs were from the SOC "General disorders and administration site conditions" (11.5% patients vs. 13.2% patients) for both of these groups of patients. The only other SOCs with an incidence of AEs ≥10% were Gastrointestinal disorders (8.3% patients vs. 12.7% patients), and Nervous system disorders (4.5% patients vs. 10.2% patients). For all other SOCs, the incidences of AEs were <10.0% for both of these groups of patients. See [Study PSMA-617-01-Table 14.3.3.3.1] for further details on AEs by SOC during the long-term follow-up in PSMA-617-01.

The incidences of AEs and high grade (≥3) AEs by PT were similar in both these groups of patients (all grades AEs: 23.3% patients vs. 25.9% patients; grade ≥3 TEAEs: 11.5% patients vs. 14.1% patients).

Of the less frequent AEs recorded during long-term follow-up, there were no reports of new malignancies, in particular, no myelodysplastic syndrome or leukemias.

The incidence of renal effects were similar in the patients who had previously been treated with ^{177}Lu-PSMA-617+BSC/BSoC as compared to those who had previously received BSC/BSoC

only (5 cases vs. 4 cases). Renal events during long-term follow-up included renal failure and acute kidney injury (2 cases each), and 1 case of blood creatinine increased in the patients who had previously been treated with ^{177}Lu-PSMA-617+BSC/BSoC.

Hepatotoxicity events were few, and events were balanced between patients who had previously received ^{177}Lu-PSMA-617+BSC/BSoC as compared to those who had previously received BSC/BSoC only

Hemorrhages, in particular intracranial hemorrhages, were few, and events were balanced between patients who had previously received ^{177}Lu-PSMA-617+BSC/BSoC as compared to those who had previously received BSC/BSoC only.

See Table 2-7 for an overview of frequent AEs by PT in at least 2% of patients in either arm during the long-term follow-up period in the PSMA-617-01 study.

See [Study PSMA-617-01–Table 14.3.3.3.2] for further details on TEAEs by PT during the long-term follow-up period.

Table 2-7 TEAEs during long-term follow-up in at least 2% of the patients by preferred term and maximum grade in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Number of patients with at least one event	**123 (23.3)**	**61 (11.5)**	**53 (25.9)**	**29 (14.1)**
Fatigue	37 (7.0)	6 (1.1)	14 (6.8)	2 (1.0)
Anaemia	34 (6.4)	14 (2.6)	15 (7.3)	8 (3.9)
Nausea	20 (3.8)	1 (0.2)	13 (6.3)	0
Thrombocytopenia	18 (3.4)	11 (2.1)	9 (4.4)	5 (2.4)
Back pain	14 (2.6)	2 (0.4)	8 (3.9)	1 (0.5)
Arthralgia	13 (2.5)	1 (0.2)	4 (2.0)	1 (0.5)
Asthenia	12 (2.3)	1 (0.2)	9 (4.4)	0
Decreased appetite	11 (2.1)	1 (0.2)	8 (3.9)	1 (0.5)
Diarrhoea	11 (2.1)	1 (0.2)	2 (1.0)	0
Vomiting	11 (2.1)	2 (0.4)	6 (2.9)	0
Oedema peripheral	10 (1.9)	0	5 (2.4)	0
Bone pain	9 (1.7)	2 (0.4)	6 (2.9)	1 (0.5)
Constipation	8 (1.5)	0	5 (2.4)	0
Dyspnoea	7 (1.3)	0	5 (2.4)	1 (0.5)
Haematuria	5 (0.9)	0	6 (2.9)	0
Headache	4 (0.8)	0	4 (2.0)	0
Weight decreased	4 (0.8)	1 (0.2)	4 (2.0)	0
Dizziness	2 (0.4)	0	6 (2.9)	0
Dyspnoea exertional	2 (0.4)	0	6 (2.9)	0
Cough	1 (0.2)	0	4 (2.0)	0
Dysgeusia	0	0	4 (2.0)	0

Source: [Study PSMA-617-01-Table 14.3.3.3.2]

TEAEs leading to fatal outcome during the long-term follow-up:

See Section 2.1.2, and Table 2-9 for details on AEs leading to fatal outcomes during the long-term follow-up period in the PSMA-617-01 study.

2.1.1.2 Overview of treatment emergent adverse events in PSMA-617-02

The safety results from the PSMA-617-02 study (SAS) were generally consistent with PSMA-617-01 study results (FAS Safety Analysis Set).

Treatment emergent adverse events by system organ class

Seven (7/71, 9.9%) patients were randomized but not treated. Rest of the 64/71 (90.1%) patients in the PSMA-617-02 study received ^{177}Lu-PSMA-617: 23 patients received 6.0 GBq, and 41 patients received 7.4 GBq.

Patients who had at least 1 TEAE (by SOC) were similar between the 2 treatment arms. Overall 61 (95.3%) patients had at least 1 TEAE: 22 (95.7%) patients in the 6.0 GBq arm, and 39 (95.1%) patients in the 7.4 GBq arm.

Overall 9 (14.1%) patients had severe TEAEs. The proportion of patients with severe events were higher in the 7.4 GBq arm (7, 17.1% patients), as compared with the 6.0 GBq arm (2, 8.7% patients).

The SOCs with TEAEs reported in at least 50% of the patients in either arm were Gastrointestinal disorders (81.3%), and the General disorders and administration site conditions (59.4% patients).

The most frequently occurring severe TEAEs were in the 7.4 GBq treatment arm and were in the Gastrointestinal disorders, and the Respiratory, thoracic and mediastinal disorders SOCs (2 patients each, 4.9%). See [Study PSMA-617-02–Section 12.2.2], [Study PSMA-617-02–Table 12-3] and [Study PSMA-617-02–Table 14.3.1.2.1].

Treatment emergent adverse events by preferred term

The numbers of patients with individual TEAEs by PT were generally balanced (within 10% difference) between the 2 treatment arms with the exceptions of dry mouth (47.8% patients in the 6.0 GBq arm vs. 63.4% patients in the 7.4 GBq arm); and diarrhea (13.0% patients in the 6.0 GBq arm vs. 31.7% patients in the 7.4 GBq arm).

See [Study PSMA-617-02–Table 14.3.1.2.1].

2.1.2 Deaths

The results from the PSMA-617-01 study and the PSMA-617-02 study were generally consistent .

2.1.2.1 Deaths in PSMA-617-01

Overall, 85 patients died while on-treatment: 66 (12.5%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 19 (9.3%) patients in the BSC/BSoC only arm.

The most frequent primary cause of death during randomized treatment in both arms was disease progression (8.3% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. 6.8% patients in the BSC/BSoC only arm). Three on-treatment deaths with AE as the primary cause of death were reported by the Investigator to be related to study treatment: 2 deaths due to pancytopenia and 1 death due to bone marrow failure, all in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The 1 patient that died due to bone marrow failure had received only 1 dose of ^{177}Lu-PSMA-617+BSC/BSoC. At the time of the patient's death, several AEs were ongoing (fatigue, pain, dyspnoea, dry mouth, thrombocytopenia, anaemia, vomiting, weight decreased, and poor quality of sleep).

See Table 2-8 for an overview of on-treatment deaths during randomized treatment (including deaths related to disease progression) and Table 2-9 for an overview of AEs with fatal outcome during the long-term follow-up period. Also see Section 2.1.3.1, and Table 2-11 for SAEs with fatal outcomes during the randomized treatment.

See [Study PSMA-617-01–Section 14.3.3] for further details.

Table 2-8 On-treatment deaths during randomized treatment (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Deaths (1)	**66 (12.5)**	**19 (9.3)**
Primary cause of death		
Disease progression	44 (8.3)	14 (6.8)
Adverse event	17 (3.2)	4 (2.0)
Unknown	3 (0.6)	0
Other	1 (0.2)	1 (0.5)
Due to COVID-19	1 (0.2)	0

(1) On-treatment deaths are deaths that occurred during randomized treatment or within 30 days of randomized treatment discontinuation.
Source: [Study PSMA-617-01-Table 14.3.14.2]

Deaths during long-term follow-up:

Seven patients in each arm had a subsequent AE with a fatal outcome during long-term follow-up. There was no apparent cluster of events or causes of death in either arm. See Table 2-9 for an overview of AEs with fatal outcomes during the long-term follow-up period.

Table 2-9 TEAEs with fatal outcomes during the long-term follow-up (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
AEs with fatal outcome	**7 (1.3)**	**7 (3.4)**
Reported in patients with primary reason for death = Adverse event	7 (1.3)	7 (3.4)
Euthanasia	2 (0.4)	0
Acute kidney injury	1 (0.2)	0
Acute respiratory failure	1 (0.2)	0

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Cardiac arrest	1 (0.2)	1 (0.5)
Haemorrhage intracranial	1 (0.2)	0
Pneumonia	1 (0.2)	0
Cerebral haemorrhage	0	1 (0.5)
Gastrointestinal haemorrhage	0	1 (0.5)
Respiratory failure	0	2 (1.0)
Sepsis	0	1 (0.5)
Suspected COVID-19	0	1 (0.5)

Source: [Study PSMA-617-01-Table 14.3.3.3.3]

2.1.2.2 Deaths in PSMA-617-02

Three (3/64, 4.7% patients) in the SAS population had TEAEs which led to death during the the randomized treatment period in PSMA-617-02 study. Also, see Section 1.2.2. Two of these deaths were considered possibly related to the drug:

- Two (2, 8.7%) patients died in the 6.0 GBq dose arm: 1 death due to a subdural hematoma 94 days after the last dose, was considered to be possibly related; and 1 death due to metastases to the central nervous system 68 days after the last dose, was determined to be unrelated.
- One (1, 2.4%) patient died in the 7.4 GBq dose arm. This death due to gastrointestinal hemorrhage and unknown causes, 72 days after the last dose, was considered to be possibly related to the study drug.

See [Study PSMA-617-02–Section 12.3 and Section 13], [Study PSMA-617-02-Table 14.3.1.1, Table 14.3.1.10.1, Table 14.3.1.9.1, Listing 16.2.12, Listing 16.2.1.1] for further details on all the deaths in PSMA-617-02 study.

2.1.3 Other treatment-emergent serious adverse events

The results from the PSMA-617-01 study and the PSMA-617-02 study were generally consistent.

2.1.3.1 Treatment-emergent serious adverse events in PSMA-617-01

In the PSMA-617-01 study, 36.3% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm; and 27.8% patients in the BSC/BSoC only arm had serious TEAEs. In keeping with the overall TEAEs, the number of patients who had serious TEAEs, including high grade serious TEAEs (grade ≥3) were generally more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

See [Study PSMA-617-01–Table 14.3.2.4.1] for further details.

Treatment-emergent serious adverse events by system organ class

The incidence of serious TEAEs by SOCs (for the majority of SOCs), were generally more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Overall, the SOCs with TEAEs reported in at least ≥5% of the patients in either arm were: infections and infestations (9.8% patients vs.

4.4% patients); nervous system disorders (6.8% patients vs. 7.8% patients); and blood and lymphatic system disorders (5.1% patients vs. 0.5% patients).

See [Study PSMA-617-01-Table 14.3.2.4.1] for further details.

Treatment-emergent serious adverse events by preferred term

The incidence of serious TEAEs and high grade serious TEAEs(grade ≥3) by PT were relatively low (<3.0% patients) in both arms, except for spinal cord compression reported in 4.9% patients in the BSC/BSoC only arm as compared to 1.1% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm (1 (0.5%) patient had a spinal cord compression event which was drug-related in the BSC/BSoC only arm). See [Study PSMA-617-01-Table 14.3.2.13.4].

See Table 2-10 for frequently reported serious TEAEs by PT and grades (≥3) in patients in either arm. Also, see [Study PSMA-617-01-Table 14.3.2.13.3] for further details.

Individual narratives for all serious TEAEs are provided in [Study PSMA-617-01-Section 14.3.3]. Additionally, the incidences of treatment-emergent safety topics of interest are discussed in Section 2.1.5.

Table 2-10 Treatment-emergent SAEs (in at least 3 patients in either arm) during randomized treatment regardless of relationship by preferred term and maximum grade in PSMA-617-01 (FAS Safety Analysis Set)

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

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grade n (%)	Grade ≥3 n (%)	All grade n (%)	Grade ≥3 n (%)
Urinary tract obstruction	4 (0.8)	4 (0.8)	0	0
Deep vein thrombosis	3 (0.6)	2 (0.4)	0	0
Infection	3 (0.6)	3 (0.6)	2 (1.0)	2 (1.0)
Ischaemic stroke	3 (0.6)	2 (0.4)	0	0
Mental status changes	3 (0.6)	2 (0.4)	0	0
Nausea	3 (0.6)	2 (0.4)	1 (0.5)	1 (0.5)
Thrombocytopenia	3 (0.6)	3 (0.6)	0	0
Urosepsis	3 (0.6)	3 (0.6)	0	0

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

Drug-related serious treatment-emergent events

Overall, 9.3% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 2.4% patients in the BSC/BSoC only arm had drug-related serious TEAEs as determined by the Investigator.

The incidence of drug-related serious TEAEs, and high grade serious TEAEs (grade ≥3) were relatively low (<3.0% patients) in both arms. See [Study PSMA-617-01-Table 14.3.2.6.1] and [Study PSMA-617-01-Table 14.3.2.13.5] for further details. Also see Section 2.1.5.1 for further details on treatment-emergent safety topics of interest.

Serious TEAEs with fatal outcomes

Note: As per the protocol progressive disease leading to fatal outcome was not to be considered; however, this was not fully clarified before implementation of amendment 3 of the protocol; see [Study PSMA-617-01-Section 9.8.1]. Two serious TEAEs of progressive disease (1 in each arm) were reported by investigators before the protocol clarification, and are presented in the table of serious TEAEs with fatal outcomes.

COVID-19 was reported as a serious TEAE E leading to a fatal outcome, while for the "on-treatment deaths" the patient who died of COVID-19 is not counted in the deaths due to TEAE. See [Study PSMA-617-01-Section 12.2.1.2.1].

Overall, 25 (3.4%) patients had serious TEAEs with fatal outcomes: 19 (3.6%) patients in the ^{177}Lu-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).

The only SAEs with fatal outcomes that were reported more than once in either arm were sepsis (4, 0.8% patients), and pancytopenia (2, 0.4% patients), and were all observed in the ^{177}Lu-PSMA-617+BSC/BSoC treatment arm. Three on-treatment deaths were reported by the Investigator to be related to study treatment: 2 deaths due to pancytopenia, and 1 death due tobone marrow failure, all in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Overall, no apparent patterns/grouping in the nature of these SAEs with fatal outcomes was observed.

Individual narratives for all SAEs are provided in [Study PSMA-617-01-Section 14.3.3]. See Table 2-11 for SAEs with fatal outcomes during the randomized treatment in PSMA-617-01 study.

Table 2-11 SAEs with fatal outcomes during randomized treatment (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
SAEs with fatal outcome	**19 (3.6)**	**6 (2.9)**
Reported in patients with primary reason for death = Disease progression	0	1 (0.5)
General physical health deterioration	0	1 (0.5)
Reported in patients with primary reason for death = Adverse event	19 (3.6)	5 (2.4)
Sepsis	4 (0.8)	0
Pancytopenia	2 (0.4)	0
Acute hepatic failure	1 (0.2)	0
Bone marrow failure	1 (0.2)	0
COVID-19	1 (0.2)	0
Disease progression	1 (0.2)	1 (0.5)
Escherichia sepsis	1 (0.2)	0
Euthanasia	1 (0.2)	0
Haemorrhage intracranial	1 (0.2)	0
Hepatic failure	1 (0.2)	0
Ischaemic stroke	1 (0.2)	0
Metastases to central nervous system	1 (0.2)	0
Multiple organ dysfunction syndrome	1 (0.2)	0
Pneumonia aspiration	1 (0.2)	0
Subdural haematoma	1 (0.2)	1 (0.5)
Arteriosclerosis	0	1 (0.5)
Cardio-respiratory arrest	0	1 (0.5)
Pneumonia	0	1 (0.5)

Source: [Study PSMA-617-01-Table 14.3.2.13.12]

2.1.3.2 Treatment-emergent serious adverse events in PSMA-617-02

In the PSMA-617-02 study, the number of patients who had at least 1 treatment-emergent SAE in the SAS population were balanced between the 2 treatment arms. Overall, 12/64 (18.8%) patients had at least 1 serious TEAE: 4 (17.4%) patients in the 6.0 GBq arm, and 8 (19.5%) patients in the 7.4 GBq arm. The most frequently reported serious TEAE overall, was metastases to the central nervous system reported in 2 (3.1%) of patients; both patients were in the 6.0 GBq arm. All other serious TEAEs (PTs) occurred in 1 patient each.

Overall, 4 (6.3%) patients in the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC; and 2 (3.1%) patients in the Gastrointestinal disorders SOC had SAEs.

See [Study PSMA-617-02-Section 12.3.2] and [Study PSMA-617-02-Table 14.3.1.4.1]. Individual narratives for all SAEs are provided in [Study PSMA-617-02-Section 14.3.3].

Drug-related treatment-emergent SAEs

Five (7.8%) patients had drug-related SAEs: 1 (4.3%) patient in the 6.0 GBq arm; and 4 (9.8%) patients in the 7.4 GBq arm; and 2 drug-related SAEs with fatal outcome. See [Study PSMA-617-02-Listing 16.2.6.1].

See [Study PSMA-617-02-Section 12.3.3.1] and [Study PSMA-617-02-Table 14.3.1.6.1] for detailed information about the drug-related SAEs in the PSMA-617-02 study.

2.1.4 Other significant adverse events

2.1.4.1 Treatment-emergent adverse events leading to discontinuation

2.1.4.1.1 Treatment-emergent adverse events leading to discontinuation in PSMA-617-01

Permanent discontinuation of ^{177}Lu-PSMA-617

Sixty-three (11.9%) patients in ^{177}Lu-PSMA-617+BSC/BSoC arm discontinued ^{177}Lu-PSMA-617 due to TEAEs. The most frequent TEAEs leading to discontinuation of ^{177}Lu-PSMA-617 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 were reported in ≤0.5% of the patients.

See Table 2-12 for TEAEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 by PT and maximum grade in the PSMA-617-01 study.

Table 2-12 TEAEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 by preferred term and maximum grade in PSMA-617-01 during randomized treatment (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**
Patients with at least one event	**63 (11.9)**	**37 (7.0)**
Anaemia	15 (2.8)	6 (1.1)
Thrombocytopenia	15 (2.8)	11 (2.1)
Leukopenia	7 (1.3)	5 (0.9)
Neutropenia	4 (0.8)	1 (0.2)
Pancytopenia	3 (0.6)	3 (0.6)
Fatigue	2 (0.4)	2 (0.4)
Haematuria	2 (0.4)	1 (0.2)
Lymphopenia	2 (0.4)	2 (0.4)
Pneumonia	2 (0.4)	1 (0.2)
Thrombotic thrombocytopenic purpura	2 (0.4)	2 (0.4)
Weight decreased	2 (0.4)	0
Acute hepatic failure	1 (0.2)	1 (0.2)
Arthralgia	1 (0.2)	1 (0.2)
Ascites	1 (0.2)	0
Blood creatinine increased	1 (0.2)	0

Preferred term	^{177}Lu-PSMA-617+BSC/BSoC N=529	
	All grades n (%)	Grade ≥3 n (%)
Bone pain	1 (0.2)	0
Disease progression	1 (0.2)	1 (0.2)
Dry mouth	1 (0.2)	0
Dyspnoea	1 (0.2)	1 (0.2)
Eye swelling	1 (0.2)	0
Fall	1 (0.2)	0
Gamma-glutamyltransferase increased	1 (0.2)	1 (0.2)
Headache	1 (0.2)	0
Metastases to central nervous system	1 (0.2)	1 (0.2)
Oedema peripheral	1 (0.2)	0
Sepsis	1 (0.2)	1 (0.2)
Skin ulcer	1 (0.2)	0
Spinal cord compression	1 (0.2)	1 (0.2)
Subdural haematoma	1 (0.2)	1 (0.2)
Urinary tract infection	1 (0.2)	1 (0.2)
Vomiting	1 (0.2)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.10]

Permanent discontinuation of BSC/BSoC

Permanent discontinuation of BSC/BSoC due to TEAEs was infrequent (45, 8.5% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 16, 7.8% patients in the BSC/BSoC only arm). Each TEAE was observed in ≤1.0% of the patients in either arm, except for spinal cord compression (1.5% patients in the BSC/BSoC only arm vs. no patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm).

See Table 2-13 for TEAEs leading to permanent discontinuation of BSC/BSoC arm by PT and maximum grade in the PSMA-617-01 study.

Table 2-13 TEAEs leading to permanent discontinuation of BSC/BSoC by preferred term and maximum grade in PSMA-617-01 during randomized treatment (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	**45 (8.5)**	**25 (4.7)**	**16 (7.8)**	**12 (5.9)**
Anaemia	5 (0.9)	4 (0.8)	0	0
Fatigue	5 (0.9)	0	0	0
Thrombocytopenia	5 (0.9)	2 (0.4)	0	0
Adrenal insufficiency	2 (0.4)	1 (0.2)	0	0
Decreased appetite	2 (0.4)	0	0	0
Leukopenia	2 (0.4)	2 (0.4)	0	0
Pancytopenia	2 (0.4)	2 (0.4)	0	0
Alanine aminotransferase increased	1 (0.2)	0	0	0

Ascites	1 (0.2)	0	0	0
Aspartate aminotransferase increased	1 (0.2)	0	0	0
Asthenia	1 (0.2)	0	0	0
Back pain	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Blood alkaline phosphatase increased	1 (0.2)	0	0	0
Cerebral haemorrhage	1 (0.2)	0	0	0
Cholestasis	1 (0.2)	1 (0.2)	0	0
Deafness	1 (0.2)	0	0	0
Delirium	1 (0.2)	0	0	0
Diarrhoea	1 (0.2)	0	0	0
Dry mouth	1 (0.2)	0	0	0
Dyspepsia	1 (0.2)	0	0	0
Dyspnoea	1 (0.2)	1 (0.2)	2 (1.0)	1 (0.5)
Failure to thrive	1 (0.2)	1 (0.2)	0	0
Gastric haemorrhage	1 (0.2)	1 (0.2)	0	0
Haemoptysis	1 (0.2)	1 (0.2)	0	0
Headache	1 (0.2)	0	0	0
Hepatocellular injury	1 (0.2)	0	1 (0.5)	0
Hypocalcaemia	1 (0.2)	1 (0.2)	0	0
Hypoglossal nerve paralysis	1 (0.2)	0	0	0
Ischaemic stroke	1 (0.2)	1 (0.2)	0	0
Myocardial infarction	1 (0.2)	1 (0.2)	0	0
Neck pain	1 (0.2)	1 (0.2)	0	0
Oedema peripheral	1 (0.2)	1 (0.2)	0	0
Oropharyngeal pain	1 (0.2)	0	0	0
Osteonecrosis	1 (0.2)	0	0	0
Pain	1 (0.2)	1 (0.2)	1 (0.5)	1 (0.5)
Skin ulcer	1 (0.2)	0	0	0
Subdural haematoma	1 (0.2)	1 (0.2)	0	0
Tumour lysis syndrome	1 (0.2)	1 (0.2)	0	0
Ventricular tachycardia	1 (0.2)	1 (0.2)	0	0
Vertigo	1 (0.2)	0	0	0
Vision blurred	1 (0.2)	0	0	0
Wound infection	1 (0.2)	1 (0.2)	0	0
Blood creatinine increased	0	0	1 (0.5)	1 (0.5)
Bone pain	0	0	2 (1.0)	1 (0.5)
Cauda equina syndrome	0	0	1 (0.5)	1 (0.5)
General physical health deterioration	0	0	1 (0.5)	1 (0.5)
Hypophosphataemia	0	0	1 (0.5)	1 (0.5)
Nausea	0	0	1 (0.5)	0
Pneumonia	0	0	1 (0.5)	1 (0.5)
Spinal cord compression	0	0	3 (1.5)	3 (1.5)
Spinal cord disorder	0	0	1 (0.5)	1 (0.5)
Urinary retention	0	0	1 (0.5)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.11]

2.1.4.1.2 Treatment-emergent adverse events leading to discontinuation in PSMA-617-02

One TEAE (abdominal pain) led to the study drug discontinuation; was reported in 1 (2.4%) patient in the 7.4 GBq arm in the SAS population.

The patient had only received 1 cycle of treatment, post which the patient was hospitalized for right-sided abdominal pain (Day 18). The patient had scans that showed PC metastases to the liver and bones, and confirmed cancer progression as the cause for this pain.

See [Study PSMA-617-02-Section 12.3.4], [Study PSMA-617-02-Table 14.3.1.8.1] and [Study PSMA-617-02-Table 14.3.1.8.2].

2.1.4.2 Treatment emergent adverse events leading to dose interruption or adjustment

2.1.4.2.1 Treatment emergent adverse events leading to dose interruption or adjustment in PSMA-617-01

TEAEs leading to dose interruption or reduction of ^{177}Lu-PSMA-617

Eighty-five (16.1%) patients in ^{177}Lu-PSMA-617+BSC/BSoC arm had TEAEs leading to dose interruptions. Of note, TEAEs leading to dose interruptions presented in Table 2-14 include TEAEs that caused the patient to miss a scheduled dose. See Section 1.2.1.

The most frequent events that led to dose interruption or reduction of ^{177}Lu-PSMA-617, were anemia (5.1% patients and 1.3% patients, respectively); and thrombocytopenia (3.6% patients and 1.9% patients, respectively). All other events that led to dose interruption or reduction were reported for ≤2.0% of the patients.

See Table 2-14 for TEAEs leading to dose interruption, and see Table 2-15 for TEAEs leading to dose reduction of ^{177}Lu-PSMA-617 in this study.

Also see [Study PSMA-617-01-Table 14.3.2.13.6] and [Study PSMA-617-01-Table 14.3.2.13.8] for further details.

Table 2-14 TEAEs leading to dose interruption of ^{177}Lu-PSMA-617 in at least 0.5% of the patients during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Patients with at least one event	**85 (16.1)**	**42 (7.9)**
Anaemia	27 (5.1)	8 (1.5)
Thrombocytopenia	19 (3.6)	8 (1.5)
Leukopenia	8 (1.5)	2 (0.4)
Neutropenia	4 (0.8)	1 (0.2)
Aspartate aminotransferase increased	3 (0.6)	1 (0.2)
Haematuria	3 (0.6)	2 (0.4)

Source: [Study PSMA-617-01-Table 14.3.2.13.8]

Table 2-15 TEAEs leading to dose reduction of ^{177}Lu-PSMA-617 by preferred term occurring in at least 0.5% of the patients during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Patients with at least one event	**30 (5.7)**	**10 (1.9)**
Thrombocytopenia	10 (1.9)	2 (0.4)
Anaemia	7 (1.3)	2 (0.4)
Dry mouth	3 (0.6)	0
Leukopenia	3 (0.6)	1 (0.2)
Neutropenia	3 (0.6)	2 (0.4)

Source: [Study PSMA-617-01-Table 14.3.2.13.6]

TEAEs leading to dose interruption or reduction of BSC/BSoC

These events were infrequent in both arms (< 2.0% for any event). See Table 2-16 for an overview of frequent TEAEs leading to dose interruption of BSC/BSoC by PT in at least 3 patients in either arm during randomized treatment; and see and Table 2-17 for an overview of TEAEs leading to dose reduction of BSC/BSoC by PT during the randomized treatment in the PSMA-617-01 study.

Also see [Study PSMA-617-01-Table 14.3.2.13.7 and Table 14.3.2.13.9] for further details.

Table 2-16 TEAEs leading to dose interruption of BSC/BSoC by preferred term in at least 3 patients in either arm during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Patients with at least one event	**50 (9.5)**	**32 (6.0)**	**14 (6.8)**	**9 (4.4)**
Anaemia	9 (1.7)	3 (0.6)	0	0
Sepsis	4 (0.8)	4 (0.8)	0	0
Nausea	3 (0.6)	1 (0.2)	1 (0.5)	0
Thrombocytopenia	3 (0.6)	2 (0.4)	0	0

Source: [Study PSMA-617-01-Table 14.3.2.13.9]

Table 2-17 TEAEs leading to dose reduction of BSC/BSoC by preferred term during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
Preferred term	**All grades n (%)**	**Grade ≥3 n (%)**	**All grades n (%)**	**Grade ≥3 n (%)**
Patients with at least one event	**17 (3.2)**	**0**	**7 (3.4)**	**0**
Fatigue	8 (1.5)	0	2 (1.0)	0
Asthenia	1 (0.2)	0	1 (0.5)	0
Blood creatinine increased	1 (0.2)	0	0	0
Cognitive disorder	1 (0.2)	0	1 (0.5)	0
Confusional state	1 (0.2)	0	0	0
Decubitus ulcer	1 (0.2)	0	0	0
Dry eye	1 (0.2)	0	0	0
Fall	1 (0.2)	0	0	0
Nausea	1 (0.2)	0	1 (0.5)	0
Stomatitis	1 (0.2)	0	0	0
Throat irritation	1 (0.2)	0	0	0
Vomiting	1 (0.2)	0	0	0
Alanine aminotransferase increased	0	0	1 (0.5)	0
Arthralgia	0	0	1 (0.5)	0
Aspartate aminotransferase increased	0	0	1 (0.5)	0
Decreased appetite	0	0	1 (0.5)	0
Disturbance in attention	0	0	1 (0.5)	0
Dyspnoea	0	0	1 (0.5)	0
Oedema peripheral	0	0	1 (0.5)	0
Transaminases increased	0	0	1 (0.5)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.7]

2.1.4.2.2 Treatment-emergent adverse events leading to reductions in PSMA-617-02

Two (4.9%) patients from the 7.4 GBq arm in the SAS population had TEAEs (1 patient each had anemia) which led to dose reduction of ^{177}Lu-PSMA-617.

See [Study PSMA-617-02-Section 12.3.5], [Study PSMA-617-02-Table 14.3.1.7.1] and [Study PSMA-617-02-Table 14.3.1.7.2] for further details on TEAEs leading to dose reductions.

2.1.5 Analysis of adverse events by organ system or syndrome

Other clinically significant AEs are summarized in this section.

There were no AEs of special interest (AESI) defined for special reporting initially; however, for the purposes of safety data analysis, safety topics of interest were defined later on a program level.

Safety topics of interest include AESI for ^{177}Lu-PSMA-617 as well as other safety topics considered standard for a comprehensive safety review. The search strategies for each safety

topic were defined in MedDRA to be broad enough to identify multiple different event terms in the database relevant for the topic, potentially across different SOCs.

Note that not all potential safety topics of interest considered at the time of programming, and listed in the source tables, are discussed as relevant topics in this document.

Safety topics of interest:

- The AEs of Fatigue, Myelosuppression, Dry Mouth, Nausea and Vomiting, and Renal Effects were thought to be AESI because of their likelihood to be associated with active anti-cancer treatment or the known mechanism of action of ^{177}Lu-PSMA-617, and are already known as safety concerns associated with ^{177}Lu-PSMA-617. Myelosuppression is an identified risk associated with ^{177}Lu-PSMA-617 (based on existing published data and observations in the clinical development program).
- Additionally, few other AEs were identified as potential safety topics of interest during the conduct of the ^{177}Lu-PSMA-617 clinical development program, either as standard topics for review or as potential risks: Hepatotoxicity, QT Prolongation, Intracranial Hemorrhage, Second Primary Malignancies, and Reproductive Toxicity. These topics of interest have not been confirmed as identified risks by clinical data.

There were no new or unexpected safety concerns raised during treatment with ^{177}Lu-PSMA-617 in the PSMA-617-01 or PSMA-617-02 studies. The results from the PSMA-617-01 and PSMA-617-02 studies were generally consistent for the safety topics of interest.

The sections below will focus primarily on data for safety topics of interest from the PSMA-617-01 study.

2.1.5.1 Safety topics of interest in PSMA-617-01

2.1.5.1.1 Overview of Safety Topics of Interest

Overall, no new or unexpected safety concern was raised during treatment with ^{177}Lu-PSMA-617 in the PSMA-617-01 study.

Treatment with ^{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. All these AESI can be attributed to the mechanism of action of ^{177}Lu-PSMA-617 or can be asscociated with active anti-cancer treatment.

Overall, some imbalances in the incidence of AESI between the treatment arms (^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC) were observed: 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). Of note, some of these events were grade ≥3 in severity, but only few events (<0.5%) led to withdrawal of ^{177}Lu-PSMA-617, except for Myelosuppression (7.0% patients). Renal Effects was reported with a similar incidence in both arms overall, (8.7% patients vs. 5.9% patients), and only one event (0.2% patients) led to withdrawal of ^{177}Lu-PSMA-617 in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

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

Second Primary Malignancies were infrequent events in both arms (2.1% patients vs. 1.0% patient), and none of the events were hematological malignancies or tumor of other exposed tissues.

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 ^{177}Lu-PSMA-617+BSC/BSoC arm.

See Table 2-18 for an overview of safety topics of interest or AESI. Also, see [Study PSMA-617-01-Table 14.3.3.4.3] for further details.

Also, see [SCS Appendix 1-Table 5] for drug-related safety topics of interest in the PSMA-617-01 study; and see [SCS Appendix 1-Table 6] for incidences of these safety topics of interest during long-term follow-up.

See [SCS Appendix 1-Table 3] and [SCS Appendix 1-Figure 1] for the data on time to first occurrence of safety topics of interest, including event probability estimates for Week 12 and Week 24 timepoints. Notable observations are summarized in the sections below.

Table 2-18 Overview of STI by category and maximum grade in PSMA-617-01 (FAS Safety Analysis Set)

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

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

2.1.5.1.2 Analysis of Safety Topics of Interest

See [Study PSMA-617-01-Table 14.3.3.4.3] for the incidences of these safety topics of interest by severity, relatedness, action taken including PTs in the PSMA-617-01 study. Also, see [SCS Appendix 1-Table 5] for drug-related safety topics of interest in the PSMA-617-01 study.

See [SCS Appendix 1-Table 6] for safety topics of interest during long-term follow-up. Overall, the incidence of AEs and high grade AEs were low and was similar in both groups of patients

during long-term follow-up (who were previously treated with ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only).

Overall, incidences of AESI during the randomized treatment period are discussed further in this section below.

Fatigue

Fatigue is the most frequently reported safety topic of interest, selected as an AESI because of its likelihood to be associated with active anti-cancer treatment, including ^{177}Lu-PSMA-617.

Fatigue was more frequently reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm (49.1% patients) as compared to the BSC/BSoC only arm (29.3% patients). Of note, high grade events (≥3) of fatigue were <10%, although these events were higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm (7.0% patients vs. 2.0% patients). Event probability estimates show higher probabilities of fatigue in the ^{177}Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm. Although it is not large, the difference remains consistent across study timepoints. See [SCS Appendix 1-Table 3] and [SCS Appendix 1-Figure 1].

At data cut-off, more patients had unresolved events (33.8% patients) than resolved (18.5% patients) in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The trend was similar in the BSC/BSoC only arm.

Events of fatigue leading to withdrawal of ^{177}Lu-PSMA-617 were infrequent (0.4%). See Table 2-19.

Table 2-19 Incidence, severity and outcome of AESI Fatigue (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	**BSC/BSoC only N=205 n (%)**
Patients with at least one event	260 (49.1)	60 (29.3)
Fatigue	228 (43.1)	47 (22.9)
Asthenia	34 (6.4)	16 (7.8)
Malaise	13 (2.5)	1 (0.5)
Lethargy	3 (0.6)	0
Cachexia	2 (0.4)	0
Decreased activity	1 (0.2)	0
Maximum grade		
Grade 3 AEs	37 (7.0)	4 (2.0)
Grade 4 AEs	0	1 (0.5)
Grade 5 AEs	0	0
Treatment-related AEs	190 (35.9)	23 (11.2)
SAEs	4 (0.8)	1 (0.5)
Action taken with PSMA-617		
Drug withdrawn	2 (0.4)	0
Dose reduced	2 (0.4)	0
Drug interrupted	2 (0.4)	0
Dose not changed/NA/unknown	258 (48.8)	60 (29.3)
Action taken with BSC/BSoC		

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Drug withdrawn	5 (0.9)	0
Dose reduced	9 (1.7)	3 (1.5)
Drug interrupted	2 (0.4)	1 (0.5)
Dose not changed/NA/unknown	248 (46.9)	56 (27.3)
AE outcome		
Recovered/resolved	98 (18.5)	9 (4.4)
Recovering/resolving	7 (1.3)	3 (1.5)
Not recovered/not resolved	179 (33.8)	54 (26.3)
Recovered/resolved with sequelae	1 (0.2)	0
Fatal	0	0
Unknown	1 (0.2)	0

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

Myelosuppression

This safety topic of interest includes multiple event terms covering all blood cell lines which are as anticipated, or known to be associated with ^{177}Lu-PSMA-617 treatment.

The mean absorbed radiation dose for ^{177}Lu-PSMA-617 in the red marrow was 0.035±0.020 Gy/GBq, which equates to a calculated estimated radiation exposure of 1.5±0.90 Gy for 6 cycles of 7.4 GBq Q6W. This cumulative radiation exposure estimate therefore is not in excess of the established radiation dose limit for EBRT of 2 Gy. See [SCP-Section 3.3.2] and [SCP-Table 3-1] for further details on dosimetry data.

The frequency of myelosuppression related events (including anemia, thrombocytopenia, lymphopenia, leukopenia) was higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm (47.4% patients) as compared to the BSC/BSoC only arm (17.6% patients). Of note, high grade (≥3) events of myelosuppression were higher in the ^{177}Lu-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 ^{177}Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm (see [SCS Appendix 1-Table 3]). The groups diverge quickly at early study timepoints, before the two curves take on parallel paths in later weeks (see [SCS Appendix 1-Figure 1]).

Three events suspected to be drug-related by the Investigator with fatal outcomes were reported, all in ^{177}Lu-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 [Medical History] 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. The Investigator reported fatigue as not related to ^{177}Lu-PSMA-617 or BSC/BSoC and the events (anaemia, thrombocytopenia, bone marrow failure) as possibly related to ^{177}Lu-PSMA-617 or BSC/BSoC. It is not clear whether he suffered

bone marrow failure as a result of ^{177}Lu-PSMA-617 treatment. Individual narratives are provided in [Study PSMA-617-01-Section 14.3.3]. Despite the confounders in these individual cases, study results do clearly show more severe events in the ^{177}Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm.At data cut-off, more patients had unresolved events (35.5% patients) than resolved (23.3% patients) in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The trend was similar in the BSC/BSoC arm. The data show that not uncommonly patients entered the study with a history of low cell counts and/or with counts below the lower level of the norm at screening. During the treatment period, myelosuppressive episodes were seen to resolve and recur. See [Study PSMA-617-01-Table 14.3.4.10.1].

Overall, the data show that these events were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. However, the persistence or recurrence of these events seen in some patients confirm that this category of AEs remain a risk in the patient population treated with ^{177}Lu-PSMA-617 and warrants careful monitoring and a readiness to delay or discontinue treatment when severely low counts are observed. The nature, rate and severity of these hematological AEs in the long-term follow-up were similar to the background experience seen in the BSC/BSoC only arm during randomized treatment.

See Table 2-20.

Table 2-20 Incidence, severity and outcome of AESI Myelosuppression in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Patients with at least one event	**251 (47.4)**	**36 (17.6)**
Anaemia	168 (31.8)	27 (13.2)
Thrombocytopenia	91 (17.2)	9 (4.4)
Lymphopenia	75 (14.2)	8 (3.9)
Leukopenia	66 (12.5)	4 (2.0)
Neutropenia	45 (8.5)	3 (1.5)
Pancytopenia	8 (1.5)	0
Febrile neutropenia	2 (0.4)	0
Bicytopenia	1 (0.2)	0
Bone marrow failure	1 (0.2)	0
Normocytic anaemia	1 (0.2)	0
Maximum grade		
Grade 3 AEs	104 (19.7)	14 (6.8)
Grade 4 AEs	17 (3.2)	0
Grade 5 AEs	3 (0.6)	0
Treatment-related AEs	215 (40.6)	10 (4.9)
SAEs	27 (5.1)	1 (0.5)
Action taken with PSMA-617		
Drug withdrawn	37 (7.0)	1 (0.5)
Dose reduced	21 (4.0)	0
....Drug interrupted	50 (9.5)	1 (0.5)
Dose not changed/NA/unknown	233 (44.0)	36 (17.6)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Action taken with BSC/BSoC		
Drug withdrawn	14 (2.6)	0
Dose reduced	0	0
Drug interrupted	12 (2.3)	0
Dose not changed/NA/unknown	246 (46.5)	36 (17.6)
AE outcome		
Recovered/resolved	123 (23.3)	16 (7.8)
Recovering/resolving	4 (0.8)	1 (0.5)
Not recovered/not resolved	188 (35.5)	26 (12.7)
Recovered/resolved with sequelae	3 (0.6)	0
Fatal	3 (0.6)	0
Unknown	3 (0.6)	0

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

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. See [SCP-Section 3.3.2] and [SCP-Table 3-1] for further details on dosimetry data. 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 ^{177}Lu-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 ^{177}Lu-PSMA-617+BSC/BSoC arm.

None of these events were of grade ≥3 severity or serious. CTCAE 5.0 grade 3 dry mouth is the inability to adequately aliment orally, necessitating tube feeding or total parental nutrition would which would markedly impact quality of life. It is positive to note that no such events were reported. Thirty (5.7%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm had grade 2 events. Grade 2 dry mouth includes moderate symptoms implying some alterations of oral intake such as copious water, other lubricants, soft or pureed foods. There are no records of artificial saliva products being administered as concomitant medication in this study, suggesting uncomplicated symptom management in these cases. See [Study PSMA-617-01- Table 14.3.11.1.2.1]. The majority (176, 33.3%) of the patients who had dry mouth in the ^{177}Lu PSMA-617+BSC/BSoC arm, had grade 1 events (defined as symptomatic but without significant alteration of diet). See [Study PSMA-617-01- Table 14.3.2.3.1]. The generally good manageability of these events are confirmed by the infrequent treatment discontinuations. ^{177}Lu-PSMA-617 dose was reduced in 3 (0.6%) patients, and was discontinued in 1 (0.2%) patient. See Table 2-21.

Other AEs that may suggest complications of dry mouth and could impact morbidity and quality of life were analysed. Dental carries was reported in 4 (0.8%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm. No patients in the BSC/BSoC only arm had these events. All 4 of these patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm with dental carries also had dry mouth reported as a TEAE. The dental caries were resolved in 3 cases of grade 1 dry mouth, and was still ongoing at the last observation in 1 patient with grade 2 dry mouth. See [Study PSMA-617-01-Table 14.3.2.13.2] and [Study PSMA-617-01-Listing 16.2.7.3].

Stomatitis was reported as an AE in 9 (1.7%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm and in no patients in the BSC/BSoC only arm. Six of these 9 patients reported dry mouth during the study (3 grade 2 cases, 3 grade 1 cases). Three of the 9 patients with stomatitis did not report dry mouth. One event of grade 3 stomatitis was also a serious TEAE and was ongoing at the last observation; however, this occurred in a patient who did not have a TEAE of dry mouth. The other events were grades 1-2 (4 resolved, 4 ongoing). See [Study PSMA-617-01-Listing 16.2.7.3].

Overall, the analysis suggests that dry mouth is a readily manageable event with little impact on morbidity and quality of life and rarely entails discontinuation of treatment. See Table 2-21 for frequencies, severities, outcomes and action taken with the study drug.

Table 2-21 Incidence, severity and outcome of AESI Dry Mouth in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	**BSC/BSoC only N=205 n (%)**
Patients with at least one event	**208 (39.3)**	**2 (1.0)**
Dry mouth	205 (38.8)	1 (0.5)
Aptyalism	2 (0.4)	0
Lip dry	2 (0.4)	1 (0.5)
Dry throat	1 (0.2)	0
Maximum grade		
Grade 3 AEs	0	0
Grade 4 AEs	0	0
Grade 5 AEs	0	0
Treatment-related AEs	194 (36.7)	1 (0.5)
SAEs	0	0
Action taken with PSMA-617		
Drug withdrawn	1 (0.2)	0
Dose reduced	3 (0.6)	0
Drug interrupted	0	0
Dose not changed/NA/unknown	205 (38.8)	2 (1.0)
Action taken with BSC/BSoC		
Drug withdrawn	1 (0.2)	0
Dose reduced	0	0
Drug interrupted	0	0
Dose not changed/NA/unknown	207 (39.1)	2 (1.0)
AE outcome		
Recovered/resolved	70 (13.2)	1 (0.5)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Recovering/resolving	8 (1.5)	0
Not recovered/not resolved	138 (26.1)	2 (1.0)
Recovered/resolved with sequelae	0	0
Fatal	0	0
Unknown	4 (0.8)	0

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

Nausea and Vomiting

Nausea and Vomiting were selected as a safety topic of interest because of their likelihood to be associated with active anti-cancer treatment, including ^{177}Lu-PSMA-617.

The frequency of these AESI were approximately twice as high in the ^{177}Lu-PSMA-617+BSC/BSoC arm (39.3% patients) as compared to the BSC/BSoC only arm (17.1% patients) as was expected.

Event probability estimates show clearly higher probabilities of nausea and vomiting in the ^{177}Lu-PSMA-617+BSC/BSoC arm than the BSC/BSoC-only arm across study timepoints.High grade events (≥3) were infrequent in either arm (1.5% patients vs. 0.5% patients). Nausea was reported approximately twice as often than Vomiting in both arms. At data cut-off, more patients had resolved events (28.9% patients) than unresolved (14.7% patients) in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The trend was similar in the BSC/BSoC only arm.

Only 1 (0.2%) patient was withdrawn from ^{177}Lu-PSMA-617 treatment due to this category of events, and another patient (1, 0.5%) patient was withdrawn from the BSC/BSoC only arm due to nausea and vomiting.

See Table 2-22.

Table 2-22 Incidence, severity and outcome of AESI Nausea and Vomiting (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Patients with at least one event	**208 (39.3)**	**35 (17.1)**
Nausea	187 (35.3)	34 (16.6)
Vomiting	100 (18.9)	13 (6.3)
Retching	1 (0.2)	0
Maximum grade		
Grade 3 AEs	8 (1.5)	1 (0.5)
Grade 4 AEs	0	0
Grade 5 AEs	0	0
Treatment-related AEs	162 (30.6)	9 (4.4)
SAEs	5 (0.9)	1 (0.5)
Action taken with PSMA-617		
Drug withdrawn	1 (0.2)	0
Dose reduced	0	0

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Drug interrupted	0	0
Dose not changed/NA/unknown	207 (39.1)	35 (17.1)
Action taken with BSC/BSoC		
Drug withdrawn	0	1 (0.5)
Dose reduced	2 (0.4)	1 (0.5)
Drug interrupted	3 (0.6)	1 (0.5)
Dose not changed/NA/unknown	207 (39.1)	33 (16.1)
AE outcome		
Recovered/resolved	153 (28.9)	23 (11.2)
Recovering/resolving	3 (0.6)	1 (0.5)
Not recovered/not resolved	78 (14.7)	18 (8.8)
Recovered/resolved with sequelae	1 (0.2)	0
Fatal	0	0
Unknown	2 (0.4)	0

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

Renal effects

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. See [SCP-Section 3.3.2], and [SCP-Table 3-1] for dosimetry data. This is close but 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).

In the PSMA-617-01 main study, with a broad search (SMQ acute renal failure), the search retrieved relevant renal events in 46 (8.7%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and in 12 (5.9%) patients in the BSC/BSoC only arm.

Despite the difference in crude incidences, the event probability estimates do not clearly differentiate between the ^{177}Lu-PSMA-617+BSC/BSoC and the BSC/BSoC-only arms across study timepoints for this broad renal event category.

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; however, SAEs were reported more frequently in the BSC/BSoC arm (3.4% patients) as compared to the ^{177}Lu-PSMA-617+BSC/BSoC arm (1.7% patients). The most frequent event term in this AESI category of “renal effects” was blood creatinine increased followed by acute kidney injury (which appears to be often synonymous with increased creatinine).

One event of renal failure was reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

More events resolved (5.5% patients) than were unresolved (3.4% patients) at data cut-off date in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The trend was similar in the BSC/BSoC arm. One (0.2%) patient was withdrawn from ^{177}Lu-PSMA-617 treatment due to this category of events. See Table 2-23 and [Study PSMA-617-01-Table 14.3.3.4.3].

Hence, despite higher radiation exposures that may occur in the kidneys of patients treated with ^{177}Lu-PSMA-617, renal toxicity did not emerge as an impactful safety concern in the

PSMA-617-01 study, consisting predominantly of low grade creatinine increases that were reversible.

Table 2-23 Incidence, severity and outcome of AESI Renal effect in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Patients with at least one event	**46 (8.7)**	**12 (5.9)**
Blood creatinine increased	28 (5.3)	5 (2.4)
Acute kidney injury	19 (3.6)	8 (3.9)
Blood urea increased	1 (0.2)	0
Proteinuria	1 (0.2)	0
Renal failure	1 (0.2)	0
Urine output decreased	1 (0.2)	1 (0.5)
Maximum grade		
Grade 3 AEs	18 (3.4)	6 (2.9)
Grade 4 AEs	0	0
Grade 5 AEs	0	0
Treatment-related AEs	18 (3.4)	0
SAEs	9 (1.7)	7 (3.4)
Action taken with PSMA-617		
Drug withdrawn	1 (0.2)	0
Dose reduced	2 (0.4)	0
Drug interrupted	2 (0.4)	0
Dose not changed/NA/unknown	42 (7.9)	12 (5.9)
Action taken with BSC/BSoC		
Drug withdrawn	0	1 (0.5)
Dose reduced	1 (0.2)	0
Drug interrupted	1 (0.2)	2 (1.0)
Dose not changed/NA/unknown	44 (8.3)	10 (4.9)
AE outcome		
Recovered/resolved	29 (5.5)	8 (3.9)
Recovering/resolving	1 (0.2)	1 (0.5)
Not recovered/not resolved	18 (3.4)	3 (1.5)
Recovered/resolved with sequelae	0	0
Fatal	0	0
Unknown	1 (0.2)	1 (0.5)

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

Other topics of interest

Hepatotoxicity

This search identified events of laboratory abnormalities as well hepatic diagnoses and systemic signs and symptoms that could be suggestive of hepatotoxicity. 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. See Table 2-18 and Table 2-24.

The most frequently reported events were from the SOC "Investigations": AST increased (4.2% patients vs. 2.4% patients). Blood ALP increased, Hyperbilirubinemia, ALT increased, and Hyperbilirubinemia were also noted. ALT increased and Hyperbilirubinemia reports were low in frequency overall, and similar in both arms.

Overall, approximately half of the patients in ^{177}Lu-PSMA-617+BSC/BSoC arm (31, 5.9% patients) had resolved outcomes, and half unresolved (30, 5.7% patients) at the data cut-off date. More events resolved in the ^{177}Lu-PSMA-617+BSC/BSoC arm as compared to the BSC/BSoC only arm; more than half of the events in BSC/BSoC only arm were unresolved at the data cut-off date.

There were 2 events with fatal outcomes (both in ^{177}Lu-PSMA-617+BSC/BSoC arm): 1 case of Acute Hepatic Failure; and 1 case of Hepatic Failure; however, they were not suspected to be drug-related by the Investigator. See [Study PSMA-617-01-Listing 16.2.7.3].

Table 2-24 Incidence, severity and outcome of safety topic Hepatotoxicity in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	**BSC/BSoC only N=205 n (%)**
Patients with at least one event	**54 (10.2)**	**16 (7.8)**
Aspartate aminotransferase increased	22 (4.2)	5 (2.4)
Blood alkaline phosphatase increased	20 (3.8)	2 (1.0)
Hypoalbuminaemia	20 (3.8)	3 (1.5)
Alanine aminotransferase increased	15 (2.8)	6 (2.9)
Hyperbilirubinaemia	7 (1.3)	3 (1.5)
Ascites	6 (1.1)	0
Gamma-glutamyltransferase increased	5 (0.9)	0
Acute hepatic failure	1 (0.2)	0
Cholestasis	1 (0.2)	1 (0.5)
Hepatic encephalopathy	1 (0.2)	0
Hepatic failure	1 (0.2)	0
Hepatic lesion	1 (0.2)	0
Hepatitis	1 (0.2)	0
Hepatocellular injury	1 (0.2)	2 (1.0)
International normalised ratio increased	1 (0.2)	1 (0.5)
Jaundice	1 (0.2)	1 (0.5)
Transaminases increased	0	2 (1.0)
Maximum grade		
Grade 3 AEs	11 (2.1)	5 (2.4)
Grade 4 AEs	2 (0.4)	0
Grade 5 AEs	2 (0.4)	0
Treatment-related AEs	21 (4.0)	6 (2.9)
SAEs	5 (0.9)	2 (1.0)
Action taken with PSMA-617		

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Drug withdrawn	3 (0.6)	1 (0.5)
Dose reduced	0	0
Drug interrupted	4 (0.8)	1 (0.5)
Dose not changed/NA/unknown	53 (10.0)	16 (7.8)
Action taken with BSC/BSoC		
Drug withdrawn	5 (0.9)	1 (0.5)
Dose reduced	0	2 (1.0)
Drug interrupted	5 (0.9)	3 (1.5)
Dose not changed/NA/unknown	50 (9.5)	11 (5.4)
AE outcome		
Recovered/resolved	31 (5.9)	7 (3.4)
Recovering/resolving	0	0
Not recovered/not resolved	30 (5.7)	10 (4.9)
Recovered/resolved with sequelae	2 (0.4)	0
Fatal	2 (0.4)	0
Unknown	1 (0.2)	0

Source: [Study PSMA-617-01-Table 14.3.3.4.3]

The other safety topics of interest events of QT Prolongation, Second Primary malignancies, Intracranial Hemorrhage and Reproductive Toxicity were infrequent; hence, no in-text tables are included here.

QT Prolongation

This safety topic of interest identifies patients with cardiac-related events that may be suggestive of QT prolongation. Of note, ECGs were not systematically performed during the randomized treatment period; however, after consideration a sub-study was designed to be conducted in a non-randomized cohort of the PSMA-617-01 study (^{177}Lu-PSMA-617+BSC/BSoC) of approximately 30 patients to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617.

No event of "QT Prolongation" was reported in the PSMA-617-01 main study. The most frequently reported term in this category was Syncope (1.3% patients in ^{177}Lu-PSMA-617+BSC/BSoC arm vs. none in BSC/BSoC only arm) was considered drug-related in a single case. One of 2 cases of Ventricular Tachycardia in the ^{177}Lu-PSMA-617+BSC/BSoC arm was considered drug-related. One fatal case of Cardio-Respiratory Arrest occurred in the BSC/BSoC only arm. See [Study PSMA-617-01-Table 14.3.3.4.3], and [SCS Appendix 1-Table 5].

^{177}Lu-PSMA-617 at the studied doses in the sub-study had no observed clinically relevant effects on QTcF. The results of the PK/QT analysis together with the preclinical cardiac safety studies indicates a negligible risk of an electrophysiological effect by ^{175}Lu-PSMA-617 and low radiation uptake in the heart. The absence of clinical findings related to QT prolongation in PSMA-617-01 sub-study, confirms that ^{177}Lu-PSMA-617 administration does not pose a cardiac risk. For clinical cardiodynamic evaluation compliant with ICH E14, ECGs and

time-matched PK were collected in the sub-study for PSMA-617-01. See [SCP-Section 3.7.1] and see [Study PSMA-617-01-Appendix 16.2.9.3].

Second Primary Malignancies

Due to the radiotoxic nature of ^{177}Lu-PSMA-617 treatment this safety topic of interest was regarded as a potential risk and events were sought with a broad MedDRA search. Overall, very few patients had such events (13, 1.8% patients); however, the incidence was slightly higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm as compared to the BSC/BSoC only arm (11, 2.1% patients vs. 2, 1.0% patients). The events were skin cancers and metastases to the brain or meninges. No hematological malignancies or tumors of other exposed tissues were reported during the randomized treatment period and during long-term follow-up data collection.

To note, a case of acute myeloid leukemia (AML) reported outside of the treatment-emergent period, after the 30-day post-treatment follow-up, but before capture of long-term follow-up events. The event was therefore not tabulated, but is contained in [Study PSMA-617-01-Listing 16.2.7.3].

Although insufficient evidence exists in the data to make a causal link between ^{177}Lu-PSMA-617 treatment and the subsequent development of second primary malignancies, the topic will continue to be monitored in the ongoing long-term extension of the PSMA-617-01 study.

See [Study PSMA-617-01-Table 14.3.3.4.3] and [SCS Appendix 1-Table 5].

Intracranial Hemorrhage

This safety topic of interest was raised as a potential risk during the PSMA-617-01 study because of the occurrence of a small number of events. Events remained infrequent and were similar across the 2 treatment arms (1.3% patients vs. 1.5% patients) in frequency and severity.

Four grade 3 cases were reported: 3 cases of subdural hematoma in the ^{177}Lu-PSMA-617+BSC/BSoC arm (0.6%), and 1 case of subdural hematoma in the BSC/BSoC only arm (0.5%). There were no grade 4 cases in this category, but 3 fatal events ocurred: 1 case of fatal hemorrhage intracranial in the ^{177}Lu-PSMA-617+BSC/BSoC arm; and 1 case each of subdural hematoma in both arms.

There appeared to be no pattern of event temporality and no consistent link to thrombocytopenia or other risk factors in the events reviewed (that were reported in PSMA-617-01). At this time, no causal relationship can be established with ^{177}Lu-PSMA-617.See [Study PSMA-617-01-Table 14.3.3.4.3] and [SCS Appendix 1-Table 5].

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. Events were sought with a broad MedDRA search including partner pregnancies. No partner pregnancies were reported during the conduct of the PSMA-617-01 study. The single event retrieved by the broad search was a vascular malformation identified in the search for congenital abnormalities, but which

had no bearing on reproduction in study participants. See [Study PSMA-617-01-Table 14.3.3.4.3] and [SCS Appendix 1-Table 5].

Lacrimal Toxicity:

As per data from dosimetry studies, the largest absorbed dose is in the lacrimal glands.

Radiation exposure to the lacrimal glands was notable in the PSMA-617-01 sub-study with a mean radiation absorbed dose of 2.1±0.47 Gy/GBq, higher than the range (0.85-1.23 Gy/GBq) reported in some literature (see [SCP-Table 5-1]) but comparable to the range reported in other literature (mean 2.1 Gy/GBq and range 0.36-3.8 Gy/GBq from Hohberg et al (2016) and Violet et al (2019). See [Study PSMA617-01-Appendix 16.2.9.4-Section 4]). Also, see [SCP-Section 3.3.2], [SCP-Table 3-1] for further details dosimetry data.

Though lacrimal toxicity was not defined as a group amongst the STIs, relevant events observed in the Study PSMA-617-01 are being analysed. Overall, the number and severity of events was low. Dry eye was reported by 16 (3.0%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 2 (1.0%) patients in the BSC/BSoC only arm. These were all grade 1 events, except for 1 grade 2 event in 1 patient in the ^{177}Lu-PSMA-617+BSC/BSoC arm Grade 1 events were defined as asymptomatic where lubricants were sufficient. Three (0.6%) patients received artificial tears as concomitant medication. See [Study PSMA-617-01-Table 14.3.11.1.2.1]. Grade 2 events were defined as symptomatic with moderate decrease in visual acuity. The single grade 2 event occurred in an [40-94]-year-old on study day 158, and was still ongoing at the latest observation. The patient had no other eye- or vision-related AEs. Overall, the analysis shows that dry eye is an uncommon event on ^{177}Lu-PSMA-617 treatment, nearly always asymptomatic and manageable with little impact on quality of life.

Other ophthalmic events reported in the study may potentially be associated with, or a complication of, lacrimal toxicity. Some of the relevant findings are being discussed below.

Blurred vision was reported by 9 (1.7%) patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and by 2 (1.0%) patients in the BSC/BSoC only arm. Two (0.4%) of these patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm had high grade (≥3) with blurred vison events. See [Study PSMA-617-01-Table 14.3.2.3.1].

Neither of these 2 patients had reported dry eye as an AE; 1 of the patients had a history of [Medical History] in the [**], and the other patient had ongoing diabetes and hypertension (the events were ongoing as of the most recent report). See [Study PSMA-617-01-Listing 16.2.7.3, Listing 16.2.4.4]. One SAE of blurred vision (grade 2) was reported by another patient 5 months after the last administration of ^{177}Lu-PSMA-617, reported to be definitely not related to ^{177}Lu-PSMA-617; BSoC medication was withdrawn. In the eye disorders SOC otherwise, cataract and visual impairment were reported by 1.3% patients each in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and by no patients (0%) in the BSC/BSoC-only arm during their participation in the study. Other eye-related events were uncommon (<1% in either arm).

2.1.5.2 Safety Topics of Interest in PSMA-617-02

2.1.5.2.1 Overview of Safety Topics of Interest

Although the earlier results of the PSMA-617-02 study did not present safety with the AESI groups defined for PSMA-617-01, corresponding results appear to be broadly comparable. No new or unexpected safety concerns were raised during the conduct of this study.

The events of Dry Mouth (57.8%), Fatigue (53.1%), and Nausea (46.9%) were the most frequently reported TEAEs overall, with no differences observed between the 2 treatment arms with the exception of Dry Mouth (47.8% in 6.0 GBq arm vs. 63.4% in 7.4 GBq arm). Notably, none of these events were severe, except 1 event of Nausea in the 7.4 GBq arm.

General incidence of Myelosuppression (anemia, thrombocytopenia, lymphopenia, leukopenia) was low:

- Overall, anemia was reported in 8 (12.5%) patients; there was an imbalance between the 2 treatment arms (4, 17.4% patients in the 6.0 GBq arm vs. 4, 9.4% patients in the 7.4 GBq arm). None of the events were severe.
- One (1.6%) patient had a grade 3 hematologic toxicity (7.4 GBq arm).
- One (1.6%) patient had a drug-related SAE of thrombocytopenia (7.4 GBq arm).
- No lymphopenia or leukopenia were observed.

One (1.6%) patient died due to a subdural hematoma which was considered possibly related to the study drug (6.0 GBq arm).

Two (3.1%) patients from the 6.0 GBq arm had metastases to the central nervous system.

Four (6.3%) patients reported dry eye as an AE; none of these events were severe.

Four (6.3%) patients had grade 3 AST and/or ALT levels above the normal ranges that were primarily explained by metastases of the cancer to the liver, and were not considered to be related to the study treatment.

The PSMA-617-02 study raised no safety concerns regarding Renal Effects, Hepatotoxicity, Second Primary Malignancies, QT Prolongation, or Reproductive Toxicity.

2.1.6 Subgroup analysis AEs during randomized treatment

See Section 5 for all the relevant subgroup analyses conducted during the randomized treatment.

2.1.7 Adverse drug reactions in the target indication

2.1.7.1 Adverse drug reactions in the target indication in PSMA-617-01

Adverse drug reactions (ADRs) of ^{177}Lu-PSMA-617 were selected through a process involving medical review of AEs from Study PSMA-617-01, but also other sources of safety information, using principles of causality assessment.

The criteria for the first screening and identification of adverse drug reaction (ADR) candidates was any AE (MedDRA PT) which occurred in ≥5% of patients treated with ^{177}Lu-PSMA-617+BSC/BSoC in the FAS Safety Anaysis Set of the PSMA-617-01 study or with a difference of ≥2% compared to the BSC/BSoC control arm. AEs with reported

frequencies of <5%, or additional AEs observed in other supporting studies (such as PSMA-617-02) and the literature, or additional data (such as designated medical events, deaths and SAEs in PSMA-617-01, AEs that led to discontinuation of ^{177}Lu-PSMA-617 in PSMA-617-01), 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. This medical review causality assessment considered Bradford-Hill criteria, exposure time to ^{177}Lu-PSMA-617, laboratory evidence, other individual case details, or literature (on safety issues, similar products, disease characteristics). Exposure-adjusted cumulative incidences were also considered during medical review of the ADRs. The frequencies of ADRs come from PSMA-617-01 only.

The most common ADRs (≥20%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSoC alone include: fatigue (43.1%), dry mouth (39.3%), nausea (35.3%), anemia (31.8%), decreased appetite (21.2%) and constipation (20.2%). The most common grade 3 to 4 ADRs (≥5%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSoC alone include: anemia (12.9%), thrombocytopenia (7.9%), lymphopenia (7.8%) and fatigue (5.9%). See Table 2-25. To note, NCI CTCAE v 4.03 was used. The frequency used the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). See Section 5 for description of the ADRs which were also safety topics of interest.

Table 2-25 Adverse drug reactions-Treatment-Emergent Adverse Events Regardless of Study Drug Relationship, by Primary SOC and ADR Group during randomized treatment in PSMA-617-01 (FAS Safety Set)

	^{177}Lu-PSMA-617 +BSC/BSoC (N=529)				BSC/BSoC only (N=205)			
Risk SOC ADR	**All grades n (%)**	**Frequency category All grades**	**Grade >=3[1] n (%)**	**Frequency category Grade >=3**	**All grades n (%)**	**Frequency category All grades**	**Grade >=3 n (%)**	**Frequency category Grade >=3**
Blood and lymphatic system disorders								
Anaemia	168 (31.8)	Very Common	68 (12.9)	Very Common	27 (13.2)	Very Common	10 (4.9)	Common
Leukopenia[2]	83 (15.7)	Very Common	22 (4.2)	Common	4 (2.0)	Common	1 (0.5)	Uncommon
Lymphopenia	75 (14.2)	Very Common	41 (7.8)	Common	8 (3.9)	Common	1 (0.5)	Uncommon
Pancytopenia[3]	9 (1.7)	Common	7 (1.3)[1]	Common	0		0	
Thrombocytopenia	91 (17.2)	Very Common	42 (7.9)	Common	9 (4.4)	Common	2 (1.0)	Uncommon
Ear and labyrinth disorders								
Vertigo	11 (2.1)	Common	0		0		0	
Eye disorders								
Dry eye	16 (3.0)	Common	0		2 (1.0)	Uncommon	0	
Gastrointestinal disorders								
Abdominal pain[7]	59 (11.2)	Very Common	6 (1.1)	Common	13 (6.3)	Common	1 (0.5)	Uncommon

Risk SOC ADR	^{177}Lu-PSMA-617 +BSC/BSoC (N=529)				BSC/BSoC only (N=205)			
	All grades n (%)	Frequency category All grades	Grade >=3[1] n (%)	Frequency category Grade >=3	All grades n (%)	Frequency category All grades	Grade >=3 n (%)	Frequency category Grade >=3
Constipation	107 (20.2)	Very Common	6 (1.1)	Common	23 (11.2)	Very Common	1 (0.5)	Uncommon
Diarrhea	100 (18.9)	Very Common	4 (0.8)	Uncommon	6 (2.9)	Common	1 (0.5)	Uncommon
Dry mouth[5]	208 (39.3)	Very Common	0		1 (0.5)	Uncommon	0	
Nausea	187 (35.3)	Very Common	7 (1.3)	Common	34 (16.6)	Very Common	1 (0.5)	Uncommon
Vomiting[6]	101 (19.1)	Very Common	5 (0.9)	Uncommon	13 (6.3)	Common	1 (0.5)	Uncommon
General disorders and administration site conditions								
Decreased appetite	112 (21.2)	Very Common	10 (1.9)	Common	30 (14.6)	Very Common	1 (0.5)	Uncommon
Fatigue	228 (43.1)	Very Common	31 (5.9)	Common	47 (22.9)	Very Common	3 (1.5)	Common
Oedema peripheral[10]	52 (9.8)	Common	2 (0.4)	Uncommon	14 (6.8)	Common	1 (0.5)	Uncommon
Pyrexia	36 (6.8)	Common	2 (0.4)	Uncommon	7 (3.4)	Common	0	
Weight decreased	57 (10.8)	Very Common	2 (0.4)	Uncommon	18 (8.8)	Common	0	
Nervous system disorders								
Dizziness	44 (8.3)	Common	5 (0.9)	Uncommon	9 (4.4)	Common	0	
Dysgeusia[4]	37 (7.0)	Common	0		3 (1.5)	Common	0	
Headache	37 (7.0)	Common	4 (0.8)	Uncommon	4 (2.0)	Common	0	
Renal and urinary disorders								
Acute kidney injury[9]	45 (8.5)	Common	17 (3.2)	Common	12 (5.9)	Common	6 (2.9)	Common
Urinary tract infection[8]	61 (11.5)	Very Common	20 (3.8)	Common	2 (1.0)	Uncommon	1 (0.5)	Uncommon

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for events contributing to an ADR is only counted under the maximum grade.
Frequency category is based on the following convention: very common (>=1/10); common (>=1/100 to <1/10); uncommon (>=1/1,000 to <1/100); rare (>=1/10,000 to <1/1,000); very rare (<1/10,000).
[1] Only includes grades 3 to 4 ADRs with the exception of pancytopenia. Grade 5 (fatal) pancytopenia was reported in 2 patients who received Pluvicto plus BSoC.
[2] Leukopenia includes leukopenia and neutropenia.
[3] Pancytopenia includes pancytopenia and bicytopenia.
[4] Dysgeusia includes dysgeusia and taste disorder.
[5] Dry mouth includes dry mouth, aptyalism and dry throat.
[6] Vomiting includes vomiting and retching.
[7] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness and gastrointestinal pain.
[8] Urinary tract infection includes urinary tract infection, cystitis and cystitis bacterial.
[9] Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure and blood urea increased.
[10] Oedema peripheral includes oedema peripheral, fluid retention and fluid overload.
Coded using MedDRA version 24.0, CTCAE version 5.0
Source: [SCS Appendix 1-Table 69]

2.2 Narratives

The narratives for on-treatment deaths, SAEs, AESI, and the AEs that led to study discontinuation are provided with each individual CSR.

3 Clinical laboratory evaluations

The clinical laboratory evaluations from the PSMA-617-01 were generally consistent with the PSMA-617-02 study results.

3.1 Overview of laboratory testing

For the PSMA-617-01 Study, local laboratories performed hematology, clinical chemistry, serum testosterone, and urinalysis testing. Laboratory values and change from baseline are summarized by visit and treatment using descriptive statistics. Shift tables of the worst on-study laboratory toxicity based on CTCAE v5.0 grading relative to baseline are presented by treatment group. For laboratory tests where grades were not defined by CTCAE, results were graded by the low/normal/high classifications based on laboratory normal ranges.

For the PSMA-617-02 Study, local clinical laboratory tests included hematology and clinical chemistry based on NCI CTCAE v4.

3.2 Clinical laboratory evaluations

3.2.1 Hematology

3.2.1.1 Hematology in PSMA-617-01

3.2.1.1.1 Hematology during randomized treatment:

Hematology abnormalities were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm inclusive of the high grade abnormalities (grade 3/4), especially for parameters such as 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). This trend aligns with the higher frequency of AEs of anemia, lymphopenia and thrombocytopenia observed in this arm (see Section 2.1.1.1.1). It should be noted that, despite these expected hematology abnormalities, anemia, lymphopenia 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. See Section 2.1.4.1.1 and [Study PSMA-617-01-Section 12.2.3].

See Table 3-1 for worst post-baseline hematology abnormalities based on CTC grades during randomized treatment in the PSMA-617-01 study.

Table 3-1 Worst post-baseline hematological abnormalities based on CTC grades during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	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]

Shifts in hematologic parameters:

Almost all patients had normal (grade 0), or low grade hematology abnormalities (grade 1 or 2) at baseline for both the treatment arms and for all hematology parameters analyzed.

^{177}Lu-PSMA-617+BSC/BSoC arm: a general trend of shifts towards higher grade abnormalities during the randomized treatment period was observed for low hemoglobin, low lymphocytes, low neutrophils and low platelets. 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.

BSC/BSoC only arm: 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 ^{177}Lu-PSMA-617+BSC/BSoC arm.

See [Study PSMA-617-01-Table 14.3.4.10.1] for shifts in hematology parameters from baseline to worst post-baseline value during randomized treatment based on CTC grades.

3.2.1.1.2 Hematology during long-term follow-up

Hematology abnormalities were similar for the patients who were previously treated with ^{177}Lu-PSMA-617 versus the patients who were not previously treated with ^{177}Lu-PSMA-617 during long-term follow-up. The higher incidences of grade 3/4 hematology abnormalities for parameters such as low lymphocytes, low hemoglobin, and low platelets observed during randomized treatment in the ^{177}Lu-PSMA-617+BSC/BSoC arm were no longer observed during long-term follow-up. Both groups of patients (those who were previously treated with ^{177}Lu-PSMA-617 versus not previously treated) presented similar incidences of hematological AEs during long-term follow-up.

See Table 3-2 for worst post-baseline hematology abnormalities based on CTC grades during long-term follow-up. Also see [Study PSMA-617-01-Table 14.3.4.14.4].

Table 3-2 Worst post-baseline hematology abnormalities based on CTC grades during long-term follow-up (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Hemoglobin - Anemia	142 (26.8)	39 (7.4)	69 (33.7)	13 (6.3)
Lymphocytes - Decreased	110 (20.8)	39 (7.4)	50 (24.4)	23 (11.2)
Platelets - Decreased	78 (14.7)	28 (5.3)	29 (14.1)	8 (3.9)
Leukocytes - Decreased	60 (11.3)	8 (1.5)	18 (8.8)	4 (2.0)
Neutrophils - Decreased	28 (5.3)	6 (1.1)	7 (3.4)	2 (1.0)
Eosinophils - Eosinophilia	2 (0.4)	0	4 (2.0)	0

Source: [Study PSMA-617-01-Table 14.3.4.14.4]

3.2.1.1.3 Hematology analysis in subgroups

Hematology abnormalities and shifts observed for the subgroups are discussed in Section 5.

3.2.1.2 Hematology in PSMA-617-02

See [Study PSMA-617-02-Section 12.4.1] for the hematology results from the PSMA-617-02 study. The hematology results were comparable with the PSMA-617-01 study results.

3.2.2 Clinical chemistry

3.2.2.1 Clinical chemistry in PSMA-617-01

3.2.2.1.1 Clincial chemistry during randomized treatment

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).

See Table 3-3 for worst post-baseline clinical chemistry abnormalities based on CTC grades during randomized treatment in the PSMA-617-01 study.

Table 3-3 Worst post-baseline biochemistry abnormalities based on CTC grades during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Lactate dehydrogenase - Increased	353 (66.7)	0	123 (60.0)	0
Albumin - Hypoalbuminemia	239 (45.2)	3 (0.6)	81 (39.5)	0
Calcium - Hypocalcemia	228 (43.1)	13 (2.5)	65 (31.7)	6 (2.9)
Sodium - Hyponatremia	202 (38.2)	4 (0.8)	51 (24.9)	2 (1.0)
Aspartate aminotransferase - Increased	165 (31.2)	6 (1.1)	43 (21.0)	2 (1.0)

	^{177}Lu-PSMA-617+BSC/BSoC N=529		BSC/BSoC only N=205	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Creatinine - Increased	157 (29.7)	5 (0.9)	47 (22.9)	1 (0.5)
Alkaline phosphatase - Increased	137 (25.9)	4 (0.8)	50 (24.4)	2 (1.0)
Potassium - Hyperkalemia	135 (25.5)	3 (0.6)	39 (19.0)	1 (0.5)
Alanine aminotransferase - Increased	104 (19.7)	8 (1.5)	30 (14.6)	2 (1.0)
Potassium - Hypokalemia	90 (17.0)	7 (1.3)	34 (16.6)	0
Sodium - Hypernatremia	60 (11.3)	0	12 (5.9)	0
Calcium - Hypercalcemia	57 (10.8)	3 (0.6)	14 (6.8)	1 (0.5)
Bilirubin - Increased	52 (9.8)	4 (0.8)	28 (13.7)	1 (0.5)
Glucose - Hypoglycemia	51 (9.6)	0	11 (5.4)	0

Source: [Study PSMA-617-01-Table 14.3.4.14.1]

Shifts in clinical chemistry parameters:

Almost all patients had normal (grade 0) or low grade clincial chemistry abnormalities (grade 1 or 2) at baseline for all biochemistry parameters analyzed in both treatment arms.

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. See [Study PSMA-617-01-Table 14.3.4.5.1] for these shifts in clinical chemistry parameters from baseline to worst post-baseline value based on CTC grades during randomized treatment.

3.2.2.1.2 Clinical chemistry during long-term follow-up

Clinical chemistry abnormalities observed during the long-term follow-up were similar to what was observed in the BSC/BSoC only arm during randomized treatment. See [Study PSMA-617-01-Table 14.3.4.14.3] for worst post-baseline clinical chemistry abnormalities based on CTC grades during long-term follow-up.

3.2.2.1.3 Clinical chemistry analysis in subgroups

Clinical chemistry abnormalities and shifts observed for the subgroups are discussed in Section 5.

3.2.2.2 Liver enzymes

3.2.2.2.1 Liver enzymes during randomized treatment

Liver function parameters were similar across both the treatment arms during the randomized treatment period. 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 saftey concerns. No patient in either arm had a constellation of values indicative of Hy's law during the randomized treatment.

See Table 3-4 for categorical analysis of hepatic laboratory values during randomized treatment in the PSMA-617-01 study.

Table 3-4 Categorical analysis of hepatic laboratory values during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Worst post-baseline values		
ALT > 3x ULN	13 (2.5)	5 (2.4)
ALT > 5x ULN	2 (0.4)	3 (1.5)
ALT > 8x ULN	0	2 (1.0)
ALT > 10x ULN	0	2 (1.0)
ALT > 20x ULN	0	0
AST > 3x ULN	37 (7.0)	12 (5.9)
AST > 5x ULN	10 (1.9)	4 (2.0)
AST > 8x ULN	2 (0.4)	3 (1.5)
AST > 10x ULN	2 (0.4)	1 (0.5)
AST > 20x ULN	1 (0.2)	0
ALT or AST > 3x ULN	43 (8.1)	15 (7.3)
ALT or AST > 5x ULN	11 (2.1)	6 (2.9)
ALT or AST > 8x ULN	2 (0.4)	4 (2.0)
ALT or AST > 10x ULN	2 (0.4)	3 (1.5)
ALT or AST > 20x ULN	1 (0.2)	0
Total bilirubin > 2x ULN	5 (0.9)	3 (1.5)
Total bilirubin > 3x ULN	3 (0.6)	0
Combined and concurrent values post-baseline		
ALT > 3x ULN & BILI > 2x ULN	2 (0.4)	1 (0.5)
AST > 3x ULN & BILI > 2x ULN	3 (0.6)	2 (1.0)
ALT or AST > 3x ULN & BILI > 2x ULN	3 (0.6)	3 (1.5)
ALT or AST > 3x ULN & BILI > 2x ULN & ALP ≥ 2x ULN	3 (0.6)	3 (1.5)
ALT or AST > 3x ULN & BILI > 2x ULN & ALP < 2x ULN	0	0

Source: [Study PSMA-617-01-Table 14.3.4.14.5]

3.2.2.2.2 Liver enzymes during long-term follow-up

Liver function parameters were similar between both the groups of patients during long-term follow-up, similar to what was observed during the randomized treatment. None of the values for any of these hepatic parameters raised any specific safety concern; and no patient in either group had a constellation of values indicative of Hy's law during the long-term follow-up.

See [Study PSMA-617-01-Table 14.3.4.14.6] for categorical analysis of hepatic laboratory values during long-term follow-up in the PSMA-617-01 study.

Analysis of serum testosterone

In both arms, almost all patients had low testosterone level at baseline as per the inclusion criteria (<50 ng/dL or <1.7 nmol/L). During the randomized treatment, 2 patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm had shifts in testosterone levels to higher values (1 case of low to high; and 1 case of low to “high and low” post-baseline); and 1 patient had a shift from

normal to low value. No shifts from low to normal testosterone levels were observed during randomized treatment.

See Table 3-5 for shifts from baseline of serum testosterone levels to worst post-baseline value based on normal ranges during randomized treatment.

Table 3-5 Serum testosterone shift table based on normal ranges during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

		Baseline	Worst post-baseline value				
Treatment		**n (%)**	**Normal n (%)**	**High only n (%)**	**Low only n (%)**	**High & low n (%)**	**Missing n (%)**
^{177}Lu-PSMA-617+ BSC/BSoC N=529	Normal	1 (0.2)	0	0	1 (100)	0	0
	High	0	0	0	0	0	0
	Low	526 (99.4)	0	1 (0.2)	510 (97.0)	1 (0.2)	14 (2.7)
	Missing	2 (0.4)	0	0	1 (50.0)	0	1 (50.0)
	Total	529 (100)	0	1 (0.2)	512 (96.8)	1 (0.2)	15 (2.8)
BSC/BSoC only N=205	Normal	0	0	0	0	0	0
	High	0	0	0	0	0	0
	Low	203 (99.0)	0	0	165 (81.3)	0	38 (18.7)
	Missing	2 (1.0)	0	0	0	0	2 (100)
	Total	205 (100)	0	0	165 (80.5)	0	40 (19.5)

Source: [Study PSMA-617-01-Table 14.3.4.9.1]

3.2.2.3 Clinical chemistry in PSMA-617-02

The clinical chemistry results were generally consistent with the PSMA-617-01 study results See [Study PSMA-617-02-Table 14.3.2.1 and Listing 16.2.7.1] for further details on clinical chemistry results in the PSMA-617-02 study.

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

The vital signs, physical findings and other observations from the PSMA-617-01 and PSMA-617-02 studies were generally consistent.

4.1 Vital signs

4.1.1 Vital signs in PSMA-617-01

No clinically relevant changes were observed in both the arms during the PSMA-617-01 study. Notable vital signs were typically observed in <10% of the patients in both arms, except for decreased weight by >10% from baseline, observed in 12.9% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

See Table 4-1 for the notable vital signs during randomized treatment in the PSMA-617-01 study.

Table 4-1 Notable vital sign during randomized treatment in PSMA-617-01 (FAS Safety Analysis Set)

Vital sign Category	^{177}Lu-PSMA-617+BSC/BSoC N=529 n (%)	BSC/BSoC only N=205 n (%)
Systolic blood pressure		
≥ 180 mmHg and increase ≥ 20 mmHg from baseline	31 (5.9)	1 (0.5)
≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	5 (0.9)	3 (1.5)
Diastolic blood pressure		
≥ 105 mmHg and increase ≥ 15 mmHg from baseline	14 (2.6)	2 (1.0)
≤ 50 mmHg and decrease ≥ 15 mmHg from baseline	20 (3.8)	3 (1.5)
Pulse rate		
≥ 100 bpm and increase >25% from baseline	49 (9.3)	8 (3.9)
≤ 50 bpm and decrease >25% from baseline	16 (3.0)	1 (0.5)
Weight		
Increase > 10% from baseline	26 (4.9)	3 (1.5)
Decrease > 10% from baseline	68 (12.9)	12 (5.9)

Source: [Study PSMA-617-01-Table 14.3.6.2]

4.1.2 Vital signs in PSMA-617-02

No clinically relevant changes were observed in the mean values during the PSMA-617-02 study when comparing post-baseline values with baseline values; and during the cycles when comparing post-treatment values with pre-treatment values.

See [Study PSMA-617-02-Section 12.5], [Study PSMA-617-02-Table 14.3.4.1.1, Table 14.3.4.2.1 and Listing 16.2.8] for further details on vital sign parameters.

4.2 Electrocardiograms

4.2.1 Electrocardiograms in PSMA-617-01

ECG was done at screening only for the PSMA-617-01 study. However, after consideration, it was decided to perform systematic collection of ECG data at baseline and after treatment with ^{177}Lu-PSMA-617. Hence, a sub-study was designed to be conducted in a non-randomized cohort of the PSMA-617-01 study (^{177}Lu-PSMA-617+BSC/BSoC) of approximately 30 patients at sites in Germany to provide a more complete assessment of the safety aspects of ^{177}Lu-PSMA-617 (dosimetry, PK, urinalysis, and ECG).

The ECG abnormalities for the PSMA-617-01 main study are presented in TEAE tables and listings in the [Study PSMA-617-01].

ECG results from the PSMA-617-01 sub-study:

For the cardiodynamic evaluation, 12-lead ECGs and PK samples were collected on Cycle 1 Day 1 prior to the administration of ^{177}Lu-PSMA-617 and at 1, 4, and 24 hours post-dose. ^{177}Lu-PSMA-617 at the studied doses had no clinically relevant effects on heart rate, PR interval, or QRS duration. One patient developed new anterior T wave inversion of unclear clinical significance.

In summary, ^{177}Lu-PSMA-617 at the studied doses had no observed clinically relevant effects on QTc or other ECG parameters. A study report addendum will accompany the main study report for PSMA-617-01. See [Study PSMA-617-01-Appendix 16.2.9.3] and see [SCP-Section 3.7.1].

4.2.2 Electrocardiograms in PSMA-617-02

No clinically significant abnormalities in the ECG results were observed in the PSMA-617-02 study. See [Study PSMA-617-02–Section 12.5.2], [Study PSMA-617-02-Table 14.3.5.1] and [Study PSMA-617-02-Listing 16.2.9] for further details on ECG data.

4.3 Other safety assessments

All safety assessments are being discussed in the relevant sections of this document. No other additional assessments were performed.

5 Safety in special groups and situations

No subgroup analysis for safety were planned in the PSMA-617-02 study, except for age (<65 age group vs. ≥65 age group) due to the small number of patients.

For the purposes of this submission, only the subgroup analyses from the PSMA-617-01 study are being discussed in the following sections.

The safety of ^{177}Lu-PSMA-617 was also evaluated extensively across relevant patient subgroups by intrinsic and extrinsic parameters including subgroups with and without NAADs at baseline; by number of cycles received; by ECOG score at baseline; by age; by race; by region, by concurrent use of NAADs, by concurrent use of radiation therapy, by concurrent use of bone sparing agents as part of BSC/BSoC treatment, by baseline eGFR level, baseline proteinuria, and by baseline eGFR and proteinuria levels; by patients with renal impairment; by presence of liver metastases at baseline; and by baseline liver parameters and hepatic impairment. The results are being discussed in details in Section 5.1 (intrinsic factors) and Section 5.2 (extrinsic factors).

Overview of results from subgroup analyses:

Overall, the differences or trends observed in the subgroup analyses (intrinsic or extrinsic) were as anticipated due to the medical nature of the factors analyzed. In general, there was no notable difference in the treatment effect in the different subgroups; and the results did not raise any safety concerns for any subgroups.

Except for concurrent use of NAAD or not at baseline, all the subgroups analyzed had low number of patients in one category or the other, for example, some subgroups being predominant in the study population (e.g. elderly White males). Hence, these subgroup analyses results should be interpreted with caution.

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; however, the shifts were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Individual results from the subgroup analyses are being discussed in the sections below.

5.1 Intrinsic factors

5.1.1 Subgroup analysis by ECOG score in PSMA-617-01

5.1.1.1 Analysis of treatment emergent adverse events

Within treatment arms, in both arms, the incidences of serious TEAEs or high grade (≥3) TEAEs were higher (>10% differences) for patients with an ECOG score of 2, which may be expected due to the worse overall physical condition of the patients with an ECOG score of 2.

These differences should nevertheless be interpreted with caution due to the very low number of patients in the ECOG score 2 groups in both arms.

See Table 5-1 for an overview of AEs by ECOG score (0 or 1 vs. 2) at baseline in the PSMA-617-01 study. Also see [Study PSMA-617-01–Section 12.2.6.3, Table 14.3.2.13.20 and Table 14.3.2.13.15] for further details.

Table 5-1 Overview of TEAEs during randomized treatment by baseline ECOG score in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	ECOG score at baseline			
	0 or 1 N=494 n (%)	2 N=35 n (%)	0 or 1 N=189 n (%)	2 N=16 n (%)
AE	485 (98.2)	34 (97.1)	156 (82.5)	14 (87.5)
Serious AE	171 (34.6)	21 (60.0)	51 (27.0)	6 (37.5)
grade 3/4/5 AE	250 (50.6)	29 (82.9)	69 (36.5)	9 (56.3)
Drug-related AE	420 (85.0)	31 (88.6)	58 (30.7)	1 (6.3)
Serious drug-related AE	42 (8.5)	7 (20.0)	5 (2.6)	0
Drug-related grade 3/4/5 AE	135 (27.3)	15 (42.9)	8 (4.2)	0
AE leading to reduction of ^{177}Lu-PSMA-617	26 (5.3)	4 (11.4)	0	0
AE leading to reduction of BSC/BSoC	15 (3.0)	2 (5.7)	6 (3.2)	1 (6.3)
AE leading to interruption of ^{177}Lu-PSMA-617	77 (15.6)	8 (22.9)	2 (1.1)	0
AE leading to interruption of BSC/BSoC	47 (9.5)	3 (8.6)	13 (6.9)	1 (6.3)
AE leading to discontinuation of ^{177}Lu-PSMA-617	57 (11.5)	6 (17.1)	1 (0.5)	0
AE leading to discontinuation of BSC/BSoC	41 (8.3)	4 (11.4)	13 (6.9)	3 (18.8)
Fatal AE	16 (3.2)	3 (8.6)	6 (3.2)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.20]

5.1.1.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed for the subgroups (ECOG score of 0 or 1, vs 2) at baseline.

Overall, the shifts to higher grades were more frequent in the patients who had baseline ECOG score of 0 or 1, vs 2 in both the arms; and these shifts were more in the ^{177}Lu-PSMA-617+BSC/BSoC arm. The shifts were more frequent for low hemoglobin, low

lymphocytes, low neutrophils, low platelets, and low leukocytes in both the subgroup categories (yes vs no).

These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4. However, these can be due to the worse overall physical condition of the patients with an ECOG score of 2 in general; and none of these abnormal values or shifts raised any specific safety concern in these subgroups.

Additionally, these differences should be interpreted with caution due to the very low number of patients in the ECOG score 2 groups in both arms.

See [Study PSMA-617-01-Table 14.3.4.10.4] for the hematology shift table during randomized treatment based on CTC grades by ECOG score at baseline in the FAS Safety Analysis Set population.

5.1.1.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed for the subgroups (ECOG score of 0 or 1, vs 2) at baseline.

Overall, the shifts to higher grades were similar between the subgroups (ECOG score of 0 or 1, vs 2); however, the shifts were more frequent in the ^{177}Lu-PSMA-617 treatment arm.

Some shifts to higher grades were observed during the treatment period; however, there was no clear trend; and none of these shifts raised any safety concern for these subgroups. Additionally, these differences should be interpreted with caution due to the very low number of patients in the ECOG score 2 groups in both arms.

See [Study PSMA-617-01-Table 14.3.4.5.4] for the chemistry shift table during randomized treatment based on CTC grades by ECOG score at baseline in the FAS Safety Analysis Set population.

5.1.2 Subgroup analysis by age group in PSMA-617-01

5.1.2.1 Analysis of treatment emergent adverse events by age group in PSMA-617-01

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). Conclusions about differences in age groups with regard to the safety of ^{177}Lu-PSMA-617 treatment should therefore be made with caution as the target population of mCRPC patients are inherently elderly, and often heavily pre-treated.

See Table 5-2 for an overview of TEAEs during randomized treatment by three age categories (<65; ≥65-<75; ≥75 years at baseline).

In both arms, the incidence of TEAEs (by most type and severity) were mostly higher in the elderly subgroups of patients (≥65-<75 years age group and ≥75 years age group), as compared to the <65 years age group; however, the differences were mostly ≤10%, with few exceptions. There was a trend of more TEAEs and more severe TEAEs with increasing patient age in both the ^{177}Lu-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). In particular, treament with ^{177}Lu-PSMA-617 did not appear to increase 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.

An analysis of important TEAEs did not reveal notable differences in the frequency and severity of events between those <65 years and those ≥65 years ([Study PSMA-617-01-Table 14.3.2.3.5]). Fatal TEAEs were low in number, even in the most elderly group of patients (≥75 years); the differences seen were not clinically meaningful

Also see [Study PSMA-617-01-Table 14.3.2.13.21 and Table 14.3.2.3.5] for further details.

Table 5-2 Overview of TEAEs during randomized treatment by age in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC			BSC/BSoC only		
	<65 Years N=142 n (%)	≥65-<75 Years N=244 n (%)	≥75 Years N=143 n (%)	<65 Years N=42 n (%)	≥65-<75 Years N=100 n (%)	≥75 Years N=63 n (%)
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)
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	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-PSMA-617	21 (14.8)	40 (16.4)	24 (16.8)	0	0	2 (3.2)
TEAE leading to interruption of BSC/BSoC	10 (7.0)	23 (9.4)	17 (11.9)	1 (2.4)	5 (5.0)	8 (12.7)
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]

5.1.2.2 Analysis of hematologic parameters

For both arms and all hematologic parameters analyzed for the age subgroups (<65; ≥65-<75; ≥75), almost all patients had normal (grade 0) or low grade hematologic abnormalities (grade 1 or 2) at baseline.

Overall, the shifts to higher grades were similar between the different age groups in both arms; however, the shifts were more frequent in the ^{177}Lu-PSMA-617 treatment arm. The shifts to higher grades were more frequent for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes. These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4; however, there was no clear trend; and none of these shifts raised any safety concerns in any of these age subgroups.

See [SCS Appendix 1-Table 59] for hematology shift table based on CTC grades by age in the FAS Safety Analysis Set population

5.1.2.3 Analysis of clinical chemistry parameters

For both arms and all the clinical chemistry parameters analyzed for the age subgroups (<65; ≥65-<75; ≥75), almost all patients had normal (grade 0) or low grade clinical chemistry abnormalities (grade 1 or 2) at baseline.

Overall, the shifts to higher grades were similar between the different age groups in both treatment arms; however, the shifts were more frequent in the ^{177}Lu-PSMA-617 treatment arm. Some shifts to higher grades were observed during the treatment period; however, there was no clear trend; and none of these shifts raised any safety concerns in any of these age subgroups .

See [SCS Appendix 1-Table 47] for chemistry shift table based on CTC grades by age in the FAS Safety Analysis Set population.

5.1.3 Subgroup analysis by race in PSMA-617-01

5.1.3.1 Analysis of treatment emergent adverse events

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 . The number of Asian patients (<10 patients per arm) and Black or African American was relatively low. Hence, these results should be interpreted with caution.

See Table 5-3 for an overview of AEs by race (White vs. Black or African American vs. Asian) in the PSMA-617-01 study. Also see [Study PSMA-617-01–Section 12.2.6.5] and [Study PSMA-617-01–Table 14.3.2.13.17] for further details.

Table 5-3 Overview of TEAEs during randomized treatment by race in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC			BSC/BSoC only		
	White N=465 n (%)	Black or African American N=34 n (%)	Asian N=9 n (%)	White N=173 n (%)	Black or African American N=19 n (%)	Asian N=8 n (%)
TEAE	456 (98.1)	34 (100.0)	8 (88.9)	146 (84.4)	14 (73.7)	6 (75.0)
Serious TEAE	171 (36.8)	10 (29.4)	3 (33.3)	50 (28.9)	5 (26.3)	2 (25.0)
Grade 3/4/5 TEAE	247 (53.1)	16 (47.1)	3 (33.3)	66 (38.2)	7 (36.8)	4 (50.0)
Drug-related TEAE	400 (86.0)	26 (76.5)	8 (88.9)	47 (27.2)	7 (36.8)	4 (50.0)
Serious drug-related TEAE	40 (8.6)	3 (8.8)	2 (22.2)	5 (2.9)	0	0
Drug-related grade 3/4/5 TEAE	132 (28.4)	9 (26.5)	2 (22.2)	6 (3.5)	1 (5.3)	1 (12.5)
TEAE leading to reduction of ^{177}Lu-PSMA-617	27 (5.8)	1 (2.9)	0	0	0	0
TEAE leading to reduction of BSC/BSoC	14 (3.0)	1 (2.9)	0	5 (2.9)	1 (5.3)	1 (12.5)
TEAE leading to interruption of ^{177}Lu-PSMA-617	69 (14.8)	8 (23.5)	3 (33.3)	2 (1.2)	0	0

	^{177}Lu-PSMA-617+BSC/BSoC			BSC/BSoC only		
	White N=465 n (%)	Black or African American N=34 n (%)	Asian N=9 n (%)	White N=173 n (%)	Black or African American N=19 n (%)	Asian N=8 n (%)
TEAE leading to interruption of BSC/BSoC	42 (9.0)	5 (14.7)	0	11 (6.4)	3 (15.8)	0
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	54 (11.6)	6 (17.6)	1 (11.1)	1 (0.6)	0	0
TEAE leading to discontinuation of BSC/BSoC	38 (8.2)	4 (11.8)	1 (11.1)	14 (8.1)	0	2 (25.0)
Fatal TEAE	16 (3.4)	0	1 (11.1)	5 (2.9)	1 (5.3)	0

Source: [Study PSMA-617-01-Table 14.3.2.13.22]

5.1.3.2 Analysis of hematologic parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all subgroups categories of race (White, Black or African American, and Asian).

Overall, the shifts to higher grades were similar between the different subgroups analysed.

Overall, greater shifts to high grade TEAEs were observed for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes; however, none of these shifts raised any safety concerns.

Additionally, these these results should be interpreted with caution as the number of Asian patients (<10 patients per arm), and Black or African American was relatively low as compared to the White patients.

See [Study PSMA-617-01-Table 14.3.4.10.6] for hematology shift table during randomized treatment based on CTC grades by race in FAS Safety Analysis Set population.

5.1.3.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all subgroups categories of race (White, Black or African American, and Asian).

Overall, the shifts were similar between the different subgroups. Some shifts to higher grades were observed for all subgroups; however, the shifts were more frequent in the ^{177}Lu-PSMA-617 treatment arm.

None of these shifts raised any safety concerns for these subgroups. These these results should be interpreted with caution as the number of Asian patients (<10 patients per arm), and Black or African American was relatively low as compared to the White patients

See [Study PSMA-617-01-Table14.3.4.5.6] for the chemistry shift table during randomized treatment based on CTC grades by race in the FAS Safety Analysis Set population.

5.1.4 Subgroup analysis by baseline eGFR level, baseline proteinuria Level, and baseline eGFR and proteinuria in PSMA-617-01

5.1.4.1 Analysis of treatment emergent adverse events

5.1.4.1.1 Overview of TEAEs by baseline eGFR

Within each treatment arm, in both arms, the differences in the incidences of TEAEs in between all the categories (normal, mild and moderate) were mostly ≤15%, with few exceptions.

In the BSC/BSoC only arm, the differences between the categories of "normal versus mild versus moderate" eGFR values at baseline were greater (≥20% differences) for the high grade TEAEs (29.5% patients vs. 38.9% vs. 54.8% patients); and the serious TEAEs (17.9% patients vs. 31.6% vs. 38.7% patients).

See Table 5-4 for an overview of TEAEs by baseline eGFR values in the PSMA-617-01 study. Also see [SCS Appendix 1-Table 24] for further details.

Table 5-4 Overview of TEAEs during randomized treatment by baseline eGFR level in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC			BSC/BSoC only		
	Normal (N=229) n (%)	Mild (N=229) n (%)	Moderate (N=69) n (%)	Normal (N=78) n (%)	Mild (N=95) n (%)	Moderate (N=31) n (%)
TEAE	226 (98.7)	223 (97.4)	68 (98.6)	62 (79.5)	78 (82.1)	29 (93.5)
Serious TEAE	71 (31.0)	90 (39.3)	29 (42.0)	14 (17.9)	30 (31.6)	12 (38.7)
Grade 3/4/5 TEAE	121 (52.8)	117 (51.1)	39 (56.5)	23 (29.5)	37 (38.9)	17 (54.8)
Drug-related TEAE	196 (85.6)	192 (83.8)	61 (88.4)	26 (33.3)	22 (23.2)	11 (35.5)
Serious drug-related TEAE	19 (8.3)	24 (10.5)	5 (7.2)	1 (1.3)	3 (3.2)	1 (3.2)
Drug-related grade 3/4/5 TEAE	69 (30.1)	59 (25.8)	20 (29.0)	3 (3.8)	4 (4.2)	1 (3.2)
TEAE leading to reduction of ^{177}Lu-PSMA-617	10 (4.4)	11 (4.8)	9 (13.0)	0	0	0
TEAE leading to reduction of BSC/BSoC	6 (2.6)	9 (3.9)	2 (2.9)	4 (5.1)	3 (3.2)	0
TEAE leading to interruption of ^{177}Lu-PSMA-617	30 (13.1)	42 (18.3)	12 (17.4)	0	1 (1.1)	1 (3.2)
TEAE leading to interruption of BSC/BSoC	18 (7.9)	23 (10.0)	9 (13.0)	5 (6.4)	3 (3.2)	6 (19.4)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	24 (10.5)	28 (12.2)	9 (13.0)	0	0	1 (3.2)
TEAE leading to discontinuation of BSC/BSoC	23 (10.0)	14 (6.1)	7 (10.1)	6 (7.7)	7 (7.4)	3 (9.7)
Fatal TEAE	8 (3.5)	8 (3.5)	3 (4.3)	4 (5.1)	2 (2.1)	0

eGFR categories are defined as follows: normal (eGFR >= 90 mL/min), mild (eGFR= 60-<90 mL/min), moderate (eGFR= 30-<60 ml/min) and severe (eGFR <30 ml/min).
Source: [SCS Appendix 1-Table 36]

5.1.4.1.2 Overview of TEAEs by baseline proteinuria

Within each treatment arm, in both arms, the differences in the incidence of TEAEs in the patients who had elevated proteinuria levels versus not (non-elevated)were mostly ≤15% with few exceptions. The differences were greater in the ^{177}Lu-PSMA-617+BSC/BSoC arm for

serious TEAEs (54.2% patients vs. 32.3% patients), and high grade TEAEs (66.7% patients vs. 50.3% patients).

Similar trend was observed for the BSC/BSoC only arm but to a lesser extent.

No other meaningful trend or pattern was observed. These results need to be interpreted with caution due to the low number of patients in the "elevated" subgroup category in both arms.

See Table 5-5 for an overview of randomized TEAEs by events by baseline proteinuria levels in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 25] for further details.

Table 5-5 Overview of TEAEs during randomized treatment by baseline proteinuria level in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Elevated (N=48) n (%)	Non-elevated (N=443) n (%)	Elevated (N=18) n (%)	Non-elevated (N=170) n (%)
TEAE	48 (100.0)	434 (98.0)	16 (88.9)	140 (82.4)
Serious TEAE	26 (54.2)	143 (32.3)	7 (38.9)	45 (26.5)
Grade 3/4/5 TEAE	32 (66.7)	223 (50.3)	8 (44.4)	62 (36.5)
Drug-related TEAE	44 (91.7)	375 (84.7)	4 (22.2)	53 (31.2)
Serious drug-related TEAE	4 (8.3)	38 (8.6)	0	5 (2.9)
Drug-related grade 3/4/5 TEAE	15 (31.3)	123 (27.8)	0	7 (4.1)
TEAE leading to reduction of ^{177}Lu-PSMA-617	3 (6.3)	25 (5.6)	0	0
TEAE leading to reduction of BSC/BSoC	2 (4.2)	14 (3.2)	0	7 (4.1)
TEAE leading to interruption of ^{177}Lu-PSMA-617	8 (16.7)	69 (15.6)	0	2 (1.2)
TEAE leading to interruption of BSC/BSoC	6 (12.5)	39 (8.8)	3 (16.7)	11 (6.5)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	8 (16.7)	52 (11.7)	0	1 (0.6)
TEAE leading to discontinuation of BSC/BSoC	4 (8.3)	40 (9.0)	2 (11.1)	12 (7.1)
Fatal TEAE	4 (8.3)	14 (3.2)	1 (5.6)	4 (2.4)

Elevated is defined as baseline proteinuria >=100mg/dl , 'Positive', '2+' ,'3+' and '4+'
Source: [SCS Appendix 1-Table 37]

5.1.4.1.3 Overview of TEAEs by baseline eGFR and proteinuria

Within each treatment arm, 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 ^{177}Lu-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.

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 ^{177}Lu-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).

This analysis has identified a small number of patients (approximately 6%) with highest baseline risk of impaired renal function, distributed across both the treatment arms. There was a tendency to higher frequencies of TEAEs in this patient subgroup. This tendency was similar in the ^{177}Lu-PSMA-617+BSC/BSoC and the BSC/BSoC only arm, particularly for serious TEAEs, grade 3-5 TEAEs, fatal TEAEs, and TEAEs leading to interruption or discontinuation of ^{177}Lu-PSMA-617 or BSC/BSoC, respectively. This suggests that, although renal impairment may bear an inherent risk of increase in AEs, treatment with ^{177}Lu-PSMA-617 does not contribute to an additional risk in patients with mild to moderate renal impairment, overall. Severe renal impairment was an exclusion criterion in the PSMA-617-01 study.

These results need to be interpreted with caution due to the low number of patients in the "impaired" subgroup category in both arms.

See Table 5-6 for an overview of randomized TEAEs by events (baseline eGFR and proteinuria) at baseline in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 26] for further details.

Table 5-6 Overview of TEAEs during randomized treatment by baseline eGFR and proteinuria status in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Impaired (N=31) n (%)	Non-impaired (N=471) n (%)	Impaired (N=14) n (%)	Non-impaired (N=182) n (%)
TEAE	31 (100.0)	462 (98.1)	13 (92.9)	149 (81.9)
Serious TEAE	21 (67.7)	155 (32.9)	7 (50.0)	48 (26.4)
Grade 3/4/5 TEAE	24 (77.4)	238 (50.5)	7 (50.0)	68 (37.4)
Drug-related TEAE	28 (90.3)	401 (85.1)	2 (14.3)	56 (30.8)
Serious drug-related TEAE	4 (12.9)	42 (8.9)	0	5 (2.7)
Drug-related grade 3/4/5 TEAE	11 (35.5)	132 (28.0)	0	8 (4.4)
TEAE leading to reduction of ^{177}Lu-PSMA-617	3 (9.7)	26 (5.5)	0	0
TEAE leading to reduction of BSC/BSoC	2 (6.5)	14 (3.0)	0	7 (3.8)
TEAE leading to interruption of ^{177}Lu-PSMA-617	5 (16.1)	74 (15.7)	0	2 (1.1)
TEAE leading to interruption of BSC/BSoC	6 (19.4)	41 (8.7)	3 (21.4)	11 (6.0)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	7 (22.6)	54 (11.5)	0	1 (0.5)
TEAE leading to discontinuation of BSC/BSoC	3 (9.7)	41 (8.7)	2 (14.3)	14 (7.7)
Fatal TEAE	4 (12.9)	14 (3.0)	1 (7.1)	5 (2.7)

Impaired is defined as baseline eGFR<90 mL/min and proteinuria >=100mg/dl , 'Positive', '2+' ,'3+' and '4+'
Source: [SCS Appendix 1-Table 38]

5.1.4.2 Analysis of hematology parameters

Hematology shifts by baseline eGFR, by baseline proteinuria, and by baseline eGFR and proteinuria

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all subgroups and parameters analyzed, for all the categories of baseline eGFR (normal, mild

and moderate); of baseline proteinuria (elevated vs. non-elevated); and of baseline eGFR and proteinuria (impaired vs. non-impaired).

Overall, the shifts to higher grades were similar between the different subgroups analysed; however, the shifts were more frequent in the ^{177}Lu-PSMA-617 treatment arm. Overall, greater shifts to high grade TEAEs were observed for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes; however, none of these shifts raised any safety concerns.

See [SCS Appendix 1-Table 60] for the hematology shift table based on CTC grades by baseline eGFR Level in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 61] for the hematology shift table based on CTC grades by baseline proteinuria levels in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 62] for the hematology shift table based on CTC grades by baseline eGFR and proteinuria levels in the FAS Safety Analysis Set population.

5.1.4.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all subgroups and parameters analyzed, for all the categories of baseline eGFR (normal, mild and moderate); of baseline proteinuria (elevated vs. non-elevated); and of baseline eGFR and proteinuria (impaired vs. non-impaired).

Overall, the shifts were similar between the different subgroups. Some shifts to higher grades were observed for all subgroups and the shifts were more frequent in the 177Lu-PSMA-617 treatment arm; however, no clear trend was observed and none of these shifts raised any safety concerns in these subgroups.

See [SCS Appendix 1-Table 48] for the chemistry shift table based on CTC grades by baseline eGFR Level in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 49] for the chemistry shift table based on CTC grades by baseline proteinuria levels in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 50] for the chemistry shift table based on CTC grades by baseline eGFR and proteinuria levels in the FAS Safety Analysis Set population.

5.1.5 Subgroup analysis by renal impairment based on medical history in PSMA-617-01

5.1.5.1 Analysis of treatment emergent adverse events

Within each treatment arm, in both arms, the incidence of TEAEs by type and severity were generally higher in the patients who had renal impairment versus not (yes vs. no); however the differences were mostly ≤20% with few exceptions.

In the ^{177}Lu-PSMA-617+BSC/BSoC arm, the differences between impaired versus non-impaired groups were greater for high grade TEAEs (81.8% patients vs. 52.1% patients), and serious TEAEs (63.6% patients vs. 35.7% patients).

Only 2 patients had renal impairment at baseline in BSC/BSoC only arm, and they had no TEAEs which were serious, of high grade or leading to remedial action with study drug.

The number of renally impaired patients, based on medical history only, is smaller than the analysis undertaken by baseline laboratory values above. The number is too small to make any observations on the BSC/BSoC-only group, but in the ^{177}Lu-PSMA-617+BSC/BSoC arm a similar observation can be made to that described in Section 5.1.4.1.3.

See Table 5-7 for an overview of randomized TEAEs by renal impairment at baseline in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 27] for further details.

Table 5-7 Overview of TEAEs during randomized treatment by renal impairment status based on medical history in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Yes (N=11) n (%)	No (N=518) n (%)	Yes (N=2) n (%)	No (N=203) n (%)
TEAE	11 (100.0)	508 (98.1)	2 (100.0)	168 (82.8)
Serious TEAE	7 (63.6)	185 (35.7)	0	57 (28.1)
Grade 3/4/5 TEAE	9 (81.8)	270 (52.1)	0	78 (38.4)
Drug-related TEAE	9 (81.8)	442 (85.3)	0	59 (29.1)
Serious drug-related TEAE	2 (18.2)	47 (9.1)	0	5 (2.5)
Drug-related grade 3/4/5 TEAE	4 (36.4)	146 (28.2)	0	8 (3.9)
TEAE leading to reduction of ^{177}Lu-PSMA-617	1 (9.1)	29 (5.6)	0	0
TEAE leading to reduction of BSC/BSoC	0	17 (3.3)	0	7 (3.4)
TEAE leading to interruption of ^{177}Lu-PSMA-617	4 (36.4)	81 (15.6)	0	2 (1.0)
TEAE leading to interruption of BSC/BSoC	3 (27.3)	47 (9.1)	0	14 (6.9)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	2 (18.2)	61 (11.8)	0	1 (0.5)
TEAE leading to discontinuation of BSC/BSoC	1 (9.1)	44 (8.5)	0	16 (7.9)
Fatal TEAE	0	19 (3.7)	0	6 (3.0)

Renal impairment is determined through search of selected PTs in Medical History. Patients with at least one event are classified as 'Yes', otherwise as 'No', regardless of the events or timing of events'
Source: [SCS Appendix 1-Table 39]

5.1.5.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all the analyzed parameters in patients who had renal impairment versus not (yes vs. no) at baseline.

The shifts to higher grades was more frequent for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes. Due to the lower number of patients in the renally impaired subgroup, it was not possible to draw any meaningful comparisions in the shifts between the subgroups.

See [SCS Appendix 1-Table 63] for the hematology shift table based on CTC grades by renal impairment based on medical history in the FAS Safety Analysis Set population.

5.1.5.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all the analyzed parameters in patients who had renal impairment versus not (yes vs. no) at baseline.

Some shifts to higher grades were observed during the treatment period; however, there was no clear trend; and none of these shifts raised any safety concerns in these subgroups.

Due to the lower number of patients in the renally impaired subgroup, it was not possible to draw any meaningful comparisions in the shifts between the subgroups.

See [SCS Appendix 1-Table 51] for the chemistry shift table based on CTC grades by renal impairment based on medical history in the FAS Safety Analysis Set population.

5.1.6 Subgroup analysis by liver metastases, liver parameters and hepatic impairment in PSMA-617-01

5.1.6.1 Analysis of treatment emergent adverse events

5.1.6.1.1 Overview of TEAEs by presence of liver metastases

Within each treatment arm, in both arms, the differences in the incidence of TEAEs in patients who had liver metastases versus not (yes vs. no) was mostly ≤15%.

No meaningful trend or pattern was observed. These results need to be interpreted with caution due to the low number of patients with liver metastases at baseline.

See Table 5-8 for an overview of randomized TEAEs by liver metastases at baseline in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 28] for further details.

Table 5-8 Overview of TEAEs during randomized treament by presence of liver metastases in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Yes (N=44) n (%)	No (N=485) n (%)	Yes (N=21) n (%)	No (N=184) n (%)
TEAE	44 (100.0)	475 (97.9)	21 (100.0)	149 (81.0)
Serious TEAE	20 (45.5)	172 (35.5)	6 (28.6)	51 (27.7)
Grade 3/4/5 TEAE	26 (59.1)	253 (52.2)	10 (47.6)	68 (37.0)
Drug-related TEAE	34 (77.3)	417 (86.0)	4 (19.0)	55 (29.9)
Serious drug-related TEAE	7 (15.9)	42 (8.7)	0	5 (2.7)
Drug-related grade 3/4/5 TEAE	18 (40.9)	132 (27.2)	1 (4.8)	7 (3.8)
TEAE leading to reduction of ^{177}Lu-PSMA-617	4 (9.1)	26 (5.4)	0	0
TEAE leading to reduction of BSC/BSoC	1 (2.3)	16 (3.3)	0	7 (3.8)
TEAE leading to interruption of ^{177}Lu-PSMA-617	7 (15.9)	78 (16.1)	1 (4.8)	1 (0.5)
TEAE leading to interruption of BSC/BSoC	4 (9.1)	46 (9.5)	0	14 (7.6)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	5 (11.4)	58 (12.0)	1 (4.8)	0
TEAE leading to discontinuation of BSC/BSoC	4 (9.1)	41 (8.5)	0	16 (8.7)
Fatal TEAE	2 (4.5)	17 (3.5)	0	6 (3.3)

Source: [SCS Appendix 1-Table 40]

5.1.6.1.2 Overview of TEAEs by liver parameters

Only 4 patients had elevated liver parameter values at baseline (ALT or AST>ULN; and BILI>ULN); however, it was decided to not include these patients for this analysis. See [SCS Appendix 1-Table 41] for an overview of randomized TEAEs by liver parameters at baseline in the FAS Safety Analysis Set population. Also see [SCS Appendix 1-Table 29] and [SCS Appendix 1-Table 2].

5.1.6.1.3 Overview of TEAEs by hepatic impairment

No patients had hepatic impairment at baseline in either arm. See [SCS Appendix 1-Table 30] for TEAEs by baseline liver parameters and PT, and [SCS Appendix 1-Table 42] for an overview of randomized TEAEs by hepatic impairment at baseline in the FAS Safety Analysis Set population.

5.1.6.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed for the categories of liver metastases (yes vs. no). Only 4 patients had elevated liver parameter values at baseline (ALT or AST>ULN; and BILI>ULN; and no patients had hepatic impairment at baseline.

No abnormal hematology identified from the data was associated with the presence of liver metastases at the baseline. Due to the lower number of patients who had liver metastases at baseline, it was not possible to draw any meaningful comparisions in the shifts between the subgroups.

See [SCS Appendix 1-Table 64] for the hematology shift table based on CTC grades by liver metastases in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 65] for the hematology shift table based on CTC grades by baseline liver parameters in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 66]for the hematology shift table based on CTC grades by hepatic impairment in the FAS Safety Analysis Set population.

5.1.6.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed for the categories of liver metastases (yes vs. no). Only 4 patients had elevated liver parameter values at baseline (ALT or AST>ULN; and BILI>ULN; and no patients had hepatic impairment at baseline.

No abnormal clinical chemistry values identified from the data was associated with the presence of liver metastases at the baseline. Due to the lower number of patients who had liver metastases at baseline, it was not possible to draw any meaningful comparisions in the shifts between the subgroups.

See [SCS Appendix 1-Table 52] for the chemistry shift table based on CTC grades by liver metastases in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 53] for the chemistry shift table based on CTC grades by baseline liver parameters in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 54] for the chemistry shift table based on CTC grades by hepatic impairment in the FAS Safety Analysis Set population.

5.2 Extrinsic factors

5.2.1 Subgroup analysis by region in PSMA-617-01

5.2.1.1 Analysis of treatment emergent adverse events by region in PSMA-617-01

Within treatment arms, in both the treatment arms, the differences in incidences of TEAEs overall, TEAEs leading to discontinuation, and fatal TEAEs were generally ≤10% for both the North American and European population.

See Table 5-9 for an overview of randomized TEAEs by region in the FAS Safety Analysis Set population. Also see [SCS Appendix 1-Table 31] and [SCS Appendix 1-Table 19].

Table 5-9 Overview of TEAEs during randomized treatment by region in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC By Region		BSC/BSoC only	
	North America N=381 n (%)	Europe N=148 n (%)	North America N=144 n (%)	Europe N=61 n (%)
TEAE	374 (98.2)	145 (98.0)	119 (82.6)	51 (83.6)
Serious TEAE	132 (34.6)	60 (40.5)	40 (27.8)	17 (27.9)
Grade 3/4/5 TEAE	198 (52.0)	81 (54.7)	55 (38.2)	23 (37.7)
Drug-related TEAE	319 (83.7)	132 (89.2)	44 (30.6)	15 (24.6)
Serious drug-related TEAE	33 (8.7)	16 (10.8)	4 (2.8)	1 (1.6)
Drug-related grade 3/4/5 TEAE	111 (29.1)	39 (26.4)	7 (4.9)	1 (1.6)
TEAE leading to reduction of ^{177}Lu-PSMA-617	20 (5.2)	10 (6.8)	0	0
TEAE leading to reduction of BSC/BSoC	15 (3.9)	2 (1.4)	5 (3.5)	2 (3.3)
TEAE leading to interruption of ^{177}Lu-PSMA-617	63 (16.5)	22 (14.9)	2 (1.4)	0
TEAE leading to interruption of BSC/BSoC	38 (10.0)	12 (8.1)	11 (7.6)	3 (4.9)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	48 (12.6)	15 (10.1)	1 (0.7)	0
TEAE leading to discontinuation of BSC/BSoC	37 (9.7)	8 (5.4)	8 (5.6)	8 (13.1)
Fatal TEAE	13 (3.4)	6 (4.1)	5 (3.5)	1 (1.6)

Source: [SCS Appendix 1-Table 31]

5.2.1.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed by region at baseline. The overall shifts in grades from baseline were generally similar for both the North American and European population.

See [SCS Appendix 1-Table 55] for hematology shift data based on CTC grades by region in the FAS Safety Analysis Set population.

5.2.1.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed by region at baseline.

The overall shifts in grades from baseline were generally similar for both the North American and European population. Some shifts to higher grades were observed during the treatment period; however, there was no clear trend; and none of these shifts raised any safety concerns for these subgroups.

See [SCS Appendix 1-Table 43] for chemistry shift data based on CTC grades by region in the FAS Safety Analysis Set population.

5.2.2 Subgroup analysis by NAAD treatment in PSMA-617-01

5.2.2.1 Analysis of treatment-emergent adverse events by NAAD treatment in at baseline

The treatment arm subgroups were classified by inclusion of NAADs (enzalutamide, abiraterone, or apalutamide) as part of assigned BSC/BSoC treatment at start of study (yes vs. no). Within treatment arms, in both the treatment arms, the differences in incidences of TEAEs overall, by type and severity were ≤10% in the presence or absence of NAAD at baseline, except for drug-related TEAEs in the BSC/BSoC only arm (39.0% patients vs. 14.9% patients).

See Table 5-10 for an overview of TEAEs by NAAD (yes vs. no) as part of assigned BSC/BSoC treatment at start of the PSMA-617-01 study in the FAS Safety Analysis Set population. Also see [Study PSMA-617-01–Section 12.2.6.1, Table 14.3.2.13.18 and Table 14.3.2.3.2] for further details.

Table 5-10 Overview of TEAEs during randomized treatment by NAAD status as part of assigned BSC/BSoC treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC		BSC/BSoC only	
	NAAD presence			
	Yes N=238 n (%)	No N=291 n (%)	Yes N=118 n (%)	No N=87 n (%)
AE	234 (98.3)	285 (97.9)	102 (86.4)	68 (78.2)
Serious AE	87 (36.6)	105 (36.1)	29 (24.6)	28 (32.2)
grade 3/4/5 AE	126 (52.9)	153 (52.6)	45 (38.1)	33 (37.9)
Drug-related AE	200 (84.0)	251 (86.3)	46 (39.0)	13 (14.9)
Serious drug-related AE	19 (8.0)	30 (10.3)	4 (3.4)	1 (1.1)
Drug-related grade 3/4/5 AE	72 (30.3)	78 (26.8)	6 (5.1)	2 (2.3)
AE leading to reduction of ^{177}Lu-PSMA-617	12 (5.0)	18 (6.2)	0	0
AE leading to reduction of BSC/BSoC	11 (4.6)	6 (2.1)	4 (3.4)	3 (3.4)
AE leading to interruption of ^{177}Lu-PSMA-617	43 (18.1)	42 (14.4)	1 (0.8)	1 (1.1)
AE leading to interruption of BSC/BSoC	35 (14.7)	15 (5.2)	8 (6.8)	6 (6.9)
AE leading to discontinuation of ^{177}Lu-PSMA-617	21 (8.8)	42 (14.4)	1 (0.8)	0
AE leading to discontinuation of BSC/BSoC	23 (9.7)	22 (7.6)	11 (9.3)	5 (5.7)
Fatal AE	8 (3.4)	11 (3.8)	4 (3.4)	2 (2.3)

Source: [Study PSMA-617-01-Table 14.3.2.13.18]

5.2.2.2 Analysis of treatment-emergent adverse events by concurrent use of NAADs as part of BSC/BSoC treatment

Concurrent use of NAAD as part of BSC/BSoC treatment (yes vs. no) was defined as having concurrent use of NAADs either at study start (on or before Cycle 1 Day 1), or at any time after study start, up until the end of treatment decision for BSC/BSoC. A pre-specified list of NAADs per WHO Drug ATC Level 4 and PT allowed as BSC/BSoC, was used to indicate and flag concurrent NAADs.

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).

No clinically relevant trend or pattern was observed. These results need to be interpreted with caution due to the low number of patients with concurrent NAAD use during randomized treatment.

See Table 5-11 for an overview of randomized TEAEs by concurrent use of NAADs as part of BSC/BSoC treatment at any time in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 20] for further details.

Table 5-11 Overview of TEAEs during randomized treatment by concurrent use of NAADs as part of BSC/BSoC treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC		BSC/BSoC only	
	Yes (N=278) n (%)	No (N=251) n (%)	Yes (N=139) n (%)	No (N=66) n (%)
TEAE	274 (98.6)	245 (97.6)	122 (87.8)	48 (72.7)
Serious TEAE	98 (35.3)	94 (37.5)	36 (25.9)	21 (31.8)
Grade 3/4/5 TEAE	147 (52.9)	132 (52.6)	54 (38.8)	24 (36.4)
Drug-related TEAE	237 (85.3)	214 (85.3)	52 (37.4)	7 (10.6)
Serious drug-related TEAE	21 (7.6)	28 (11.2)	5 (3.6)	0
Drug-related grade 3/4/5 TEAE	84 (30.2)	66 (26.3)	8 (5.8)	0
TEAE leading to reduction of ^{177}Lu-PSMA-617	14 (5.0)	16 (6.4)	0	0
TEAE leading to reduction of BSC/BSoC	13 (4.7)	4 (1.6)	6 (4.3)	1 (1.5)
TEAE leading to interruption of ^{177}Lu-PSM-617	51 (18.3)	34 (13.5)	1 (0.7)	1 (1.5)
TEAE leading to interruption of BSC/BSoC	39 (14.0)	11 (4.4)	10 (7.2)	4 (6.1)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	30 (10.8)	33 (13.1)	1 (0.7)	0
TEAE leading to discontinuation of BSC/BSoC	28 (10.1)	17 (6.8)	14 (10.1)	2 (3.0)
Fatal TEAE	8 (2.9)	11 (4.4)	4 (2.9)	2 (3.0)

Source: [SCS Appendix 1-Table 32]

5.2.2.3 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed by NAAD (yes vs. no) as part of assigned BSC/BSoC at start of study and by concurrent use of NAADs as part of BSC/BSoC treatment.

The overall shifts in grades from baseline during randomized treatment by the presence or absence of NAAD (yes vs. no) at baseline, and by concurrent use of NAAD or not (yes vs. no) were similar for both treatment arms; however, the shifts were more in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The shifts were more frequent for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes in both the subgroup categories (yes vs no). These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4; however, none of these shifts raised any safety concerns in these subgroups.

See [Study PSMA-617-01-Table 14.3.4.10.2] for the hematology shift table during randomized treatment based on CTC grades by NAAD as part of assigned BSC/BSoC at baseline in the FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 56] for hematology shift data based on CTC grades by concurrent use of NAADs as part of BSC/BSoC treatment during the randomized treatment in the FAS Safety Analysis Set population.

5.2.2.4 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed all parameters analyzed by NAAD (yes vs. no) as part of assigned BSC/BSoC at start of study, and by concurrent use of NAADs as part of BSC/BSoC treatment.

The overall shifts in grades from baseline during randomized treatment by the presence or absence of NAAD (yes vs. no) at baseline, and by concurrent use of NAAD or not (yes vs. no) were similar in both treatment arms; however, the shifts were more in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

During treatment, some shifts to higher grades were observed; however, none of these shifts raised any safety concern in these subgroups.

See [Study PSMA-617-01-Table 14.3.4.5.2] for the chemistry shift table during randomized treatment based on CTC grades by NAAD as part of assigned BSC/BSoC at baseline in the FAS Safety FAS Safety Analysis Set population.

See [SCS Appendix 1-Table 44] for chemistry shift data based on CTC grades by concurrent use of NAADs as part of BSC/BSoC treatment during the randomized treatment in the FAS Safety Analysis Set population.

5.2.3 Subgroup analysis by number of cycles in PSMA-617-01

5.2.3.1 Analysis of treatment-emergent adverse events

There was no trend to increase in incidences of TEAEs by type or severity in patients who received more cycles of ^{177}Lu-PSMA-617 (the differences were mostly ≤15%). Conversely, a higher proportion of patients experienced serious TEAEs, high grade TEAEs, fatal TEAEs, or

TEAEs leading to a remedial action with the study drug in patients receiving ≤4 cycles of ^{177}Lu-PSMA-617. Nevertheless, ≥50% patients proceeded to receive 5-6 cycles, and hence, overall, there was no suggestion of a safety concern in patients who received more cycles of ^{177}Lu-PSMA-617.

See Table 5-12 for an overview of randomized TEAEs by ^{177}Lu-PSMA-617 cycles received in the FAS Safety Analysis Set population. See [Study PSMA-617-01Table 14.3.2.13.19] and [Study PSMA-617-01-Table 14.3.2.13.14] for further details.

Table 5-12 Overview of TEAEs during randomized treatment by Lu-PSMA-617 cycles received in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617+BSC/BSoC	
	<= 4 cycles (N=240) n (%)	**5-6 cycles (N=289) n (%)**
TEAE	234 (97.5)	285 (98.6)
Serious TEAE	100 (41.7)	92 (31.8)
grade 3/4/5 TEAE	145 (60.4)	134 (46.4)
Drug-related TEAE	205 (85.4)	246 (85.1)
Serious drug-related TEAE	33 (13.8)	16 (5.5)
Drug-related grade 3/4/5 TEAE	88 (36.7)	62 (21.5)
TEAE leading to reduction of ^{177}Lu-PSMA-617	14 (5.8)	16 (5.5)
TEAE leading to reduction of BSC/BSoC	6 (2.5)	11 (3.8)
TEAE leading to interruption of ^{177}Lu-PSMA-617	61 (25.4)	24 (8.3)
TEAE leading to interruption of BSC/BSoC	29 (12.1)	21 (7.3)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	50 (20.8)	13 (4.5)
TEAE leading to discontinuation of BSC/BSoC	34 (14.2)	11 (3.8)
Fatal TEAE	13 (5.4)	6 (2.1)

Source: [Study PSMA-617-01-Table 14.3.2.13.19]

5.2.3.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed in patients who received ≤4 cycles and those who received 5-6 cylcles of ^{177}Lu-PSMA-617).

Greater shifts to higher grade TEAEs were observed decreased blood cell counts (low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes), however, the shifts to higher grades were similar between the subgroups analysed (patients who received ≤4 cycles vs. those who received 5-6 cycles of ^{177}Lu-PSMA-617). Receiving more cycles of ^{177}Lu-PSMA-617 was not associated with an increased hematological risk.

Greater shifts to high grade TEAEs were observed for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes; however, none of these shifts raised any safety concerns in these subgroups.

See [Study PSMA-617-01-Table 14.3.4.10.3] for hematology shift table during randomized treatment based on CTC grades by number of ^{177}Lu-PSMA-617 cycles in the FAS Safety Analysis Set population.

5.2.3.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed in patients who received ≤4 cycles and those who received 5-6 cylcles of ^{177}Lu-PSMA-617).

Some shifts to higher grades were observed during the treatment period; however, there was no clear trend. No abnormal clinical chemistry values or shifts identified from the data raised any safety concerns associated with a higher number of ^{177}Lu-PSMA-617 treatment cycles.

See [Study PSMA-617-01-Table 14.3.4.5.3] for chemistry shift table during randomized treatment based on CTC grades by number of ^{177}Lu-PSMA-617 in the FAS Safety Analysis Set population.

5.2.4 Subgroup analysis by concurrent use of radiation therapy as part of BSC/BSoC treatment in PSMA-617-01

5.2.4.1 Analysis of treatment emergent adverse events

Within each treatment arm, in both arms, the difference in the incidence of TEAEs was generally ≤10% in patients who had concurrent treatment with radiation therapy versus not (yes vs. no), with few exceptions. The differences in the serious TEAEs, and higher grade TEAEs were greater (≥15% differences) in the "yes" category versus "no" in both arms.

Few patients required concurrent radiation therapyin both the treatment arms; however, as observed overall, the incidence of TEAEs were higher in the ^{177}Lu-PSMA-617+BSoC than in the BSoC-only arm.

Irrespective of drug relatedness, there was a slight preponderance of serious TEAEs and higher grade TEAEs (≥15% differences) in the "yes" category versus "no" in both arms.

No clinically meaningful trends or pattern were observed. These results need to be interpreted with caution due to the low number of patients with concurrent use of radiation therapy at baseline.

See Table 5-13 for an overview of randomized TEAEs by concurrent use of radiation therapy as part of BSC/BSoC treatment in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 33] for further details.

Table 5-13 Overview of TEAEs during randomized teratment by concurrent use of radiation therapy as part of BSC/BSoC treatment in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Yes (N=69) n (%)	No (N=460) n (%)	Yes (N=29) n (%)	No (N=176) n (%)
TEAE	69 (100.0)	450 (97.8)	29 (100.0)	141 (80.1)
Serious TEAE	34 (49.3)	158 (34.3)	12 (41.4)	45 (25.6)
Grade 3/4/5 TEAE	47 (68.1)	232 (50.4)	16 (55.2)	62 (35.2)
Drug-related TEAE	57 (82.6)	394 (85.7)	9 (31.0)	50 (28.4)
Serious drug-related TEAE	7 (10.1)	42 (9.1)	1 (3.4)	4 (2.3)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Yes (N=69) n (%)	No (N=460) n (%)	Yes (N=29) n (%)	No (N=176) n (%)
Drug-related grade 3/4/5 TEAE	20 (29.0)	130 (28.3)	2 (6.9)	6 (3.4)
TEAE leading to reduction of ^{177}Lu-PSMA-617	2 (2.9)	28 (6.1)	0	0
TEAE leading to reduction of BSC/BSoC	2 (2.9)	15 (3.3)	0	7 (4.0)
TEAE leading to interruption of ^{177}Lu-PSMA-617	10 (14.5)	75 (16.3)	0	2 (1.1)
TEAE leading to interruption of BSC/BSoC	10 (14.5)	40 (8.7)	4 (13.8)	10 (5.7)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	4 (5.8)	59 (12.8)	0	1 (0.6)
TEAE leading to discontinuation of BSC/BSoC	6 (8.7)	39 (8.5)	4 (13.8)	12 (6.8)
Fatal TEAE	4 (5.8)	15 (3.3)	0	6 (3.4)

Source: [SCS Appendix 1-Table 33]

5.2.4.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed at baseline.

The shifts to higher grades were comparatively greater in the group of patients who had concurrent treatment with radiation therapy. The shifts were more frequent for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes; however, none of these shifts raised any safety concerns.

See [SCS Appendix 1-Table 57] for the hematology shift data, based on CTC grades by concurrent use of radiation therapy as part of BSC/BSoC treatment at any time in the FAS Safety Analysis Set population.

5.2.4.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed at baseline. Generally, only few shifts to higher grades were observed during treatment. Although, the shifts to higher grades were comparatively greater in the group of patients who had concurrent treatment with radiation therapy, none of these shifts raised any safety concerns.

See [SCS Appendix 1-Table 45] for chemistry shift data based on CTC grades by concurrent use of radiation therapy as part of BSC/BSoC treatment at any time in the FAS Safety Analysis Set population.

5.2.5 Subgroup analysis by concurrent use of bone sparing agents as part of BSC/BSoC treatment in PSMA-617-01

5.2.5.1 Analysis of treatment emergent adverse events

Within each treatment arm, the incidence of TEAEs was generally ≤10% between patients who had concurrent treatment with bone sparing agents versus not (yes vs. no).

See Table 5-14 for an overview of randomized TEAEs by concurrent use of bone sparing agents as part of BSC/BSoC treatment in the FAS Safety Analysis Set population. See [SCS Appendix 1-Table 34] for further details.

Table 5-14 Overview of TEAEs during randomized treatment by concurrent use of bone-sparing agents as part of BSC/BSoC in PSMA-617-01 (FAS Safety Analysis Set)

	^{177}Lu-PSMA-617 +BSC/BSoC		BSC/BSoC only	
	Yes (N=229) n (%)	No (N=300) n (%)	Yes (N=107) n (%)	No (N=98) n (%)
TEAE	226 (98.7)	293 (97.7)	90 (84.1)	80 (81.6)
Serious TEAE	81 (35.4)	111 (37.0)	32 (29.9)	25 (25.5)
Grade 3/4/5 TEAE	125 (54.6)	154 (51.3)	43 (40.2)	35 (35.7)
Drug-related TEAE	199 (86.9)	252 (84.0)	31 (29.0)	28 (28.6)
Serious drug-related TEAE	18 (7.9)	31 (10.3)	4 (3.7)	1 (1.0)
Drug-related grade 3/4/5 TEAE	63 (27.5)	87 (29.0)	5 (4.7)	3 (3.1)
TEAE leading to reduction of ^{177}Lu-PSMA-617	14 (6.1)	16 (5.3)	0	0
TEAE leading to reduction of BSC/BSoC	7 (3.1)	10 (3.3)	1 (0.9)	6 (6.1)
TEAE leading to interruption of ^{177}Lu-PSMA-617	34 (14.8)	51 (17.0)	1 (0.9)	1 (1.0)
TEAE leading to interruption of BSC/BSoC	22 (9.6)	28 (9.3)	8 (7.5)	6 (6.1)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	20 (8.7)	43 (14.3)	1 (0.9)	0
TEAE leading to discontinuation of BSC/BSoC	20 (8.7)	25 (8.3)	10 (9.3)	6 (6.1)
Fatal TEAE	5 (2.2)	14 (4.7)	2 (1.9)	4 (4.1)

Source: [SCS Appendix 1-Table 34]

5.2.5.2 Analysis of hematology parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed at baseline.

Overall, the shifts to higher grades were similar between the patients who had concurrent treatment with bone sparing agents versus not (yes vs. no). The shifts were more frequent for low hemoglobin, low lymphocytes, low neutrophils, low platelets, and low leukocytes in both the subgroup categories (yes vs no) in both treatment arms; however, the shifts were more in the ^{177}Lu-PSMA-617+BSC/BSoC arm. These shifts were mainly by 1 or 2 grades up, with some shifts to grade 4; however, none of these shifts raised any safety concerns in these subgroups.

See [SCS Appendix 1-Table 58] for hematology shift table based on CTC grades by concurrent use of bone sparing agents as part of BSC/BSoC treatment at any time in the FAS Safety Analysis Set population.

5.2.5.3 Analysis of clinical chemistry parameters

Most patients in both arms had normal (grade 0) or low grade abnormalities (grade 1 or 2) for all parameters analyzed at baseline.

Some shifts to higher grades were observed during treatment. Overall, the shifts to higher grades were similar between the patients who had concurrent treatment with bone sparing agents versus not (yes vs. no) in both treatment arms; none of these shifts raised any particular safety concerns in these subgroups.

See [SCS Appendix 1-Table 46] for chemistry shift table based on CTC grades by concurrent use of bone sparing agents as part of BSC/BSoC treatment at any time in the FAS Safety Analysis Set population.

5.3 Drug interactions

As ^{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, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions. ^{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. See [SCP-Section 3.5].

5.4 Use in pregnancy and lactation

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 177Lu-PSMA-617 in pregnant or lactating women. However, based on its mechanism of action, all radiopharmaceuticals, including 177Lu-PSMA-617, can cause fetal harm. Study PSMA-617-01 had no reports of partner pregnancies during the randomized treatment period or the long-term follow-up period.

There are no human or animal studies conducted to determine the effects of ^{177}Lu-PSMA-617 on fertility.

However, dosimetry data from the PSMA-617-01 sub-study could be utilized to estimate potential effects on male fertility with ^{177}Lu-PSMA-617 treatment. The mean radiation absorbed dose to the testes was 0.023 Gy/GBq, which could result in an estimated mean radiation exposure of 0.17 Gy from a single 7.4 GBq dose and an estimated cumulative mean radiation exposure of 1.02 Gy from six total 7.4 GBq doses. Therefore, for the range of 1 to 6 doses of exposure to ^{177}Lu-PSMA-617 treatment, the threshold for temporary male sterility (0.15 Gy) could may be exceeded (International Commission on Radiological Protection 2007) and ^{177}Lu-PSMA-617 may cause temporary infertility. If the maximum radiation absorbed dose to the testes (0.14 Gy/GBq) is considered, this could result in an estimated radiation exposure of 1.04 Gy from a single 7.4 GBq dose and an estimated cumulative radiation exposure of 6.22 Gy from six total 7.4 GBq doses. Therefore, for the range of 1 to 6 doses of exposure to ^{177}Lu-PSMA-617 treatment, the threshold for permanent male sterility (3.5-6.0 Gy) may possibly be exceeded (International Commission on Radiological Protection 2007) and the possibility that treatment with ^{177}Lu-PSMA-617 may cause permanent infertility cannot be ruled out. Thus, it can be concluded that the recommended cumulative dose of 44.4 GBq of ^{177}Lu-PSMA-617 results in a radiation absorbed dose to the testes within the range where ^{177}Lu-PSMA-617 may cause infertility [SCP-Section 3.1].

Because of its mechanism of action, male patients should use condoms for intercourse during treatment with ^{177}Lu-PSMA-617 and for 14 weeks after the last dose. The proposed contraception timeframe after stopping treatment is based on 5 times the effective half-life

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

5.5 Overdose

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. ^{177}Lu-PSMA-617 doses as high as 9.3 GBq have been administered in early phase dose-ranging clinical trials as known from literature, and no dose-limiting toxicities were observed (Rathke et al (2018)).

Additionally, the possibility of an overdose of ^{177}Lu-PSMA-617 is unlikely, as the single-dose vial used contains a predefined amount of radioactivity (recommended dose of 7.4 GBq (±0.10), and is under control of and administered by healthcare providers who are qualified by specific training and experience.

In the event of administration of a radiation overdose with ^{177}Lu-PSMA-617, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body (by frequent micturition or by forced diuresis and frequent bladder voiding), and the effective dose that was applied should be estimated.

5.6 Drug abuse

There is no known potential for drug abuse with ^{177}Lu-PSMA-617, which is handled and administered only by medical personnel authorized to handle radiopharmaceuticals in designated clinical settings.

5.7 Withdrawal and rebound

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

5.8 Effects on ability to drive or operate machinery or impairment of mental ability

No studies have been performed on the effects of ^{177}Lu-PSMA-617 on the ability to drive or operate machinery. However, based on the nature of the AEs reported in study PSMA-617-01 (such as fatigue and dizziness), it is expected that ^{177}Lu-PSMA-617 has no or negligible influence on the ability to drive and use machines.

6 Postmarketing data

6.1 Worldwide literature search

No publications are available for ^{177}Lu-PSMA-617 from Endocyte/Novartis-sponsored studies.

A worldwide scientific and medical literature search was performed using Embase (covering both EMBASE and MEDLINE databases) from 01 January 2018 to 12 Mar 2021.

Publications meeting the following search terms: "^{177}Lu-PSMA" or "^{177}Lu-DKFZ-PSMA-617" or "^{177}Lu-PSMA-DKFZ-617" or "Lu-177-DKFZ-PSMA-617" or " ^{177}Lu-labeled PSMA-617" or "[177Lu]Lu-PSMA-617" or "^{177}-Lu-DKFZ-617-PSMA" or "prostate specific membrane antigen Lu 177" or "prostate specific membrane antigen 617 Lu 177" or "prostate specific membrane antigen" or "lutetium 177" or "J5912, 2TX591" or "225-Ac-PSMA-R2" or "PSMA-SR6" or "225-Ac-PSMA -SR6" or "PSMA-Ab" or "225-Ac-PSMA -Ab" or "227-Th-PSMA-Ab" or "Actimab-P" or "RPS-070" or "225-Ac-RPS-0702" or "THG-005" were closely reviewed for new and important safety information.

Notably, Huang et al (2019) observed the development of clinical tumor lysis syndrome (TLS) in patients treated by RLT with ^{177}Lu. This study was a retrospective database search of patients undergoing RLT with ^{177}Lu-DOTATATE, -DOTATOC, or PSMA-617 conducted between February 2011 and December 2017. Among 539 RLTs performed on 205 patients with activities ranging from 4.9 to 7.5 GBq of ^{177}Lu, four patients (0.74% of RLT cycles, 1.9% of patients) developed clinical TLS. The authors concluded that TLS is a rare but definite complication of RLT, suggesting that patient monitoring for TLS should be mandatory.

Based on a cumulative clinical database review performed by Endocyte, as of 10 June 2019, and incremental reviews since then till 12 Mar 2021, 2 patients with diagnosed TLS were identified. Among them, the first patient developed symptoms prior to initiation of therapy with ^{177}Lu-PSMA-617, while the other discontinued from the study with no additional information available. One additional patient was identified with recorded serious event of acute kidney injury and combination of symptoms indicative of TLS, but the criteria for establishing clinical diagnosis were not met. In 3 other patients, recorded adverse events were assessed as non-serious and were reversible. Overall, as of today there is insufficient data to confirm an association between TLS and ^{177}Lu-PSMA-617 and to classify TLS as potential risk of ^{177}Lu-PSMA-617.

There were no other new or emerging safety signals for ^{177}Lu-PSMA-617 from the scientific literature during the period of 01-Jan-2018 to 12-Mar-2021.

6.2 Post-marketing surveillance

^{177}Lu-PSMA-617 has not received marketing authorization in any country.

7 Conclusion

Overall, 734 patients from the PSMA-617-01 main study, 30 patients from the PSMA-617-01 sub-study; and 64 patients from the Study PSMA-617-02 were evaluable for safety for the purpose of this submission.

Safety conclusions from PSMA-617-01:

Of the 831 patients randomized in the study PSMA-617-01, 551 were randomized to ^{177}Lu-PSMA-617+BSC/BSoC arm, and 280 to the BSC/BSoC only arm, of which, 529 patients received at least 1 dose of ^{177}Lu-PSMA-617, and 205 patients received at least 1 dose of BSC/BSoC.

Demographics and disease characteristics: 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.

TEAEs: Overall, the TEAEs were usually more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Given the longer exposure time in that arm (mean duration of exposure: 7.9 vs. 3.5 months), these higher incidences of TEAEs might in part be related to the longer duration of exposure to randomized treatment.

The biggest differences (at least 20% differences) between the 2 treatment arms (^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) at the level of MedDRA SOC were observed for: Gastrointestinal disorders (75.4% patients vs. 31.7% patients); General disorders and administration site conditions (61.2% patients vs. 38.5% patients); and Blood and lymphatic system disorders (47.8% patients vs. 18.0% patients).

High grade TEAEs (grade ≥3):

In both arms, the grade ≥3 TEAEs were relatively infrequent (<5.0% in either arms) except for myelosuppression events (anemia, thrombocytopenia, and lymphopenia) in the ^{177}Lu-PSMA-617+BSC/BSoC arm. These events of myelosuppression are already anticipated TEAEs for ^{177}Lu-PSMA-617. It may be 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% patients.

Non-hematological TEAEs: Similarly, although the TEAEs such as dry mouth, nausea, diarrhea, vomiting and UTI were also more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm, 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

Drug-related TEAEs (as assessed by the Investigator): These were 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). The high grade (≥3) events that were reported with highest incidence in this arm were anemia (9.6% patients), thrombocytopenia and lymphopenia (6.8% each) . Of note, dry mouth, fatigue and nausea, that were the most reported drug-related events in this arm, were usually low grade (≤2) in severity. The imbalance of drug-related AEs, as assessed by the Investigator, should 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.

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

Serious TEAEs: In both arms, each serious TEAE was reported with a frequency <3.0%, except for spinal cord compression reported in 4.9% patients in the BSC/BSoC only arm versus 1.1% patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Discontinuations: 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 ^{177}Lu-PSMA-617+BSC/BSoC arm were anemia, fatigue, thrombocytopenia (0.9% patients each), which were all also observed in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Dose interruptions and reductions: The most frequent TEAEs that led to dose interruption or reduction of ^{177}Lu-PSMA-617 were anemia (5.1% and 1.3%, respectively); and thrombocytopenia (3.6% and 1.9%, respectively). All other events leading to interruption or reduction of ^{177}Lu-PSMA-617 were reported in less than 2.0% of patients each. TEAEs leading to dose interruption or reduction of BSC/BSoC were relatively infrequent (<2.0% for any event in both arms).

Safety topics of interest: These included AESI for ^{177}Lu-PSMA-617, as well as other topics considered standard for a comprehensive safety review. Upon close examination, none of the safety topics of interest raised a new or not yet known safety concern.

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), were selected as AESI because of their likelihood to be associated with active anti-cancer treatment or the known mechanism of action of ^{177}Lu-PSMA-617; and as they were already known events associated with ^{177}Lu-PSMA-617. Of note, some of these events were high grade (≥grade3), but only few events (<0.5%) led to withdrawal from ^{177}Lu-PSMA-617 treatment, except for Myelosuppression (7.0% patients).

Renal Effects was selected as an AESI because of the likelihood to be associated with the known mechanism of action and distribution of ^{177}Lu-PSMA-617. These events were reported with a similar incidence in both treatment arms (8.7% patients vs. 5.9% patients); and only 1 (0.2%) event led to withdrawal from ^{177}Lu-PSMA-617+BSC/BSoC.

Hepatotoxicity was reported with a similar incidence (less than 5% differences) in both arms (10.2% patients vs. 7.8% patients), and very few events led to withdrawal from ^{177}Lu-PSMA-617+BSC/BSoC (0.6% patients).

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

Second Primary Malignancies were infrequent events in both arms (2.1% patients vs. 1.0% patients), and none of the events were hematological malignancy or tumor of other exposed tissues.

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 none provided evidence of a safety concern or tolerability issues.

Clinical hematology: Hematology abnormalities were more frequent and usually of higher grade in the ^{177}Lu-PSMA-617+BSC/BSoC arm, as reflected in the incidences of TEAEs related to myelosuppression. Of note, during long-term follow-up, these hematology abnormalities in the ^{177}Lu-PSMA-617+BSC/BSoC arm returned to similar incidences and severity to what was seen in the BSC/BSoC only arm. Generally, the shifts from baseline values to higher grades for hematology abnormalities was more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm (mainly by 1 or 2 grades up, with some shifts to grade 4), as compared to the BSC/BSoC only arm (shifts were lower and with relatively fewer or no shifts to grade 3 or 4).

Overall, there were no safety concerns or any special risk identified for any of the subpgroups analyzed. The hematology results from the subgroups should be interpreted with caution as the subgroups analyzed were imbalanced in term of number of patients.

Clinical chemistry: Clinical chemistry abnormalities and categorical analysis of hepatic laboratory values were similar in both arms. For both arms and all parameters analyzed for subgroups, almost all patients had normal (grade 0) or low grade clinical chemistry abnormalities (grade 1 or 2) at baseline. During treatment, only few shifts to higher grades were observed; No trend was observed and none of these abnormalities and shifts raised any safety concerns.

Overall, there were no safety concerns or any special risks identified for any of the subgroups analyzed. The clinical chemistry results from the subgroups should be interpreted with caution as the subgroups analyzed were imbalanced in term of number of patients.

Vital signs and ECG: Notable vital signs for blood pressure, pulse rate and weight during randomized treatment were typically observed in <10% patients, except for a weight decrease by >10% from baseline observed in 12.9% patients in ^{177}Lu-PSMA-617+BSC/BSoC arm as compared with 5.9% patients in BSC/BSoC only arm.

Thirty patients in the sub-study received 7.4 GBq ^{177}Lu-PSMA-617+BSC/BSoC and were evaluated for ECG parameters. ^{177}Lu-PSMA-617 at the studied doses had no observed clinically relevant effects on heart rate, PR interval, or QRS duration. One patient developed new anterior T wave inversion of unclear clinical significance. The primary and secondary analyses demonstrated no clinically relevant effects of ^{177}Lu-PSMA-617 on QTcF. In summary, ^{177}Lu-PSMA-617 at the studied dose had no clinically relevant effects on QTc or other ECG parameters.

Long-term follow-up: Safety data that was collected from patients in the long-term follow-up, after end-of-treatment, did not reveal any new safety concerns. The nature, rate and severity of AEs in the long-term follow-up were similar to what was reported in the BSC/BSoC only arm during randomized treatment.

Subgroup analyses: The safety of ^{177}Lu-PSMA-617 was also evaluated extensively across relevant patient subgroups including subgroups with and without NAADs at baseline, number of cycles received, ECOG score at baseline, age, race, region, concurrent use of NAADs, concurrent use of radiation therapy, concurrent use of bone sparing agents as part of BSC/BSoC treatment, baseline eGFR level, baseline proteinuria, baseline eGFR and proteinuria levels, patients with renal impairment, presence of liver metastases at baseline and baseline liver parameters.

Overall, the differences or trends observed in the subgroup analyses (intrinsic or extrinsic) were as anticipated due to the medical nature of the factors analyzed. The subgroup analyses results did not raise any particular safety concerns for any of the subgroups analyzed.

Except for concurrent use of NAAD or not at baseline, all the subgroups analyzed had low number of patients in one category or the other, for example, some subgroups being predominant in the study population (e.g. elderly White males). No formal statistical test of hypotheses were performed for any of the subgroup analyses. Hence, these results from the subgroup analyses should be interpreted with caution.

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 treatment arms; however, the shifts were more in the ^{177}Lu-PSMA-617+BSC/BSoC arm, probably due to the longer duration of exposure in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Most of the subgroups analyzed had low number of patients in one category or the other. Hence, these results should be interpreted with caution.

Overall conclusion from PSMA-617-01: The study demonstrated acceptable safety and tolerability of ^{177}Lu-PSMA-617, with no new or unexpected safety concerns emerging during treatment randomized treatment or during long-term follow-up.

The safety profile was consistent with data previously reported, and was well tolerated and manageable with appropriate clinical intervention. The most frequent non-hematological and myelosuppression events observed during treatment with ^{177}Lu-PSMA-617 are as expected and already known as safety concerns associated with ^{177}Lu-PSMA-617 treatment from published experience. These can be attributed to the mechanism of action of ^{177}Lu-PSMA-617 which increases the risk of fatigue, dry mouth, nausea and vomiting, and myelosuppression; however, these events were manageable with supportive care and with occasional delays in treatment cycles.

Renal effects, that could also be expected due to the renal expression of PSMA and route of excretion, were of a lower frequency and were mainly "increases in serum creatinine" that allowed continued treatment and were mostly reversible. Higher grade events and serious TEAEs of acute renal failure were no more likely to occur when treated with ^{177}Lu-PSMA-617 than with BSC/BSoC only.

Overall, 10.2% of patients randomized to the ^{177}Lu-PSMA-617+BSC/BSoC arm discontinued treatment with ^{177}Lu-PSMA-617 due to an AE at some point during the study, showing a largely tolerable treatment profile.

AESI that resulted in the highest frequency of discontinuations of ^{177}Lu-PSMA-617 was myelosuppression (7.0% of patients); all other events, including fatigue and dry mouth, led to discontinuation in <0.6% of patients each. Safety data that was collected from patients in the long-term follow-up, after end-of-treatment, did not reveal any new safety concerns. The increased risk of fatigue, dry mouth, myelosuppression, and nausea and vomiting observed during treatment in the ^{177}Lu-PSMA-617+BSC/BSoC arm was transient, and was similar to the background experience seen in the BSC/BSoC only arm during the long-term follow-up.

The nature, rate and severity of AEs in the long-term follow-up were similar to the background experience seen in the BSC/BSoC only arm during randomized treatment. Notably, long-term follow-up did not show long-term toxicity such as renal effects or second primary malignancies.

The safety results suggest that ^{177}Lu-PSMA-617+BSC/BSoC represents a novel, effective and well tolerated regimen in PSMA-positive patients with mCRPC who were previously treated with 1-2 taxanes and at least 1 NAAD.

Safety conclusions from PSMA-617-02: Overall, 64 patients were evaluable for toxicity and safety in the PSMA-617-02 study; 23 patients received 6.0 GBq dose of ^{177}Lu-PSMA-617, and 41 patients received 7.4 GBq dose of ^{177}Lu-PSMA-617. This imbalance can be attributed to the early termination of the study.

In general, the patients with any event were similar in all severity between the treatment arms (95.7% patients in the 6.0 GBq arm vs. 95.1% patients in the 7.4 GBq arm); and slightly higher in the 7.4 GBq arm when compared with the 6.0 GBq arm for severe events (17.1% patients vs. 8.7% patients).

The most common TEAEs in the 6.0 GBq treatment arm and the 7.4 GBq treatment arm were dry mouth, fatigue, nausea, diarrhea, constipation, vomiting, taste disorder, pain, and anemia.

Seven (7, 9.9% patients) died during this study, i.e., from enrollment through 24 months of follow-up: 4 (14.3%) patients in the 6.0 GBq dose arm; and 3 (7.0%) patients in the 7.4 GBq dose arm. Three of these were fatal TEAEs: 3 deaths were due to unrelated AEs occurring 30 days after the last dose of ^{177}Lu-PSMA-617; and 1 death occurred in a patient prior to receiving the first dose of ^{177}Lu-PSMA-617.

There were no clinically significant changes in vital signs or ECGs in the 2 treatment arms.

Renal toxicity was not a concern. No trend in creatinine increase was observed during the study. The kidney dosimetry caveat of the dosing procedures were considered unnecessary and deleted from the protocol at the implementation of Study Protocol Amendment 1 on 07 January 2017.

No emerging hepatic concern was observed. Four patients had abnormalities (grade 3 AST and/or ALT levels above the normal ranges) that were primarily explained by metastases of the cancer to the liver and were not considered to be related to the study treatment. ALP mean values over time during treatment had no substantial change, but individual patients had variable increase or decrease of ALP that was compatible with the disease. During follow-up, the number of patients was too small to draw any meaningful conclusion.

No trend of increasing frequency of shifts from normal to abnormal over time for any hematologic parameter was observed. Overall hematology findings for the patient population showed no relevant differences between the groups. The data must be interpreted with caution due to the small number of patients with data at some of the timepoints.

These safety results are as expected for ^{177}Lu-PSMA-617 in this class of patients and support the safety results from the PSMA-617-01 study.

Overall conclusion from PSMA-617-02: The safety profile of 177Lu-PSMA-617 in this study was as anticipated based on the mechanism of action and is generally consistent with and in support of the PSMA-617-01 study results. Overall, 177Lu-PSMA-617 was well-tolerated irrespective of the dose, and no new or unexpected safety concerns emerged during treatment.

Overall Conclusions: The safety profile of 177Lu-PSMA-617 based on the results from the 2 prospective studies (PSMA-617-01 and PSMA-617-02) was as anticipated based on the mechanism of action and is generally consistent with previous 177Lu-PSMA-617 experiences as documented in literature in similar populations of patients with mCRPC.

To note, the baseline characteristics of the mCRPC patients in these studies reflect a heavily pretreated frail, elderly population with mCRPC who have high bone and visceral disease burden, who were receiving BSC/BSoC before randomization. These points are important to consider while assessing patient toxicities during treatment.

- The most frequent non-hematologic drug-related TEAEs (≥5%) with ^{177}Lu-PSMA-617 treatment were dry mouth, fatigue, nausea, decreased appetite, vomiting, diarrhea, and constipation. Of these most of the AESI - were non-specific and can be attributed to the administration of therapeutic levels of radioactive compound.
- The most frequent myelosuppression-related events/hematological toxicities were anemia, thrombocytopenia, lymphopenia, leukopenia and neutropenia, which may be attributed to the effects of ionizing radiation on sensitive pre-cursor cells in circulation or in the bone marrow close to bone metastatic lesions, but which may also be impacted by bone marrow impairment at baseline.
- The observed TEAEs were predominantly grade 1/2, reversible and most frequently seen as salivary gland, hematological and gastrointestinal toxicity.
- The incidence of grade 3/4 TEAEs was very low, and mainly restricted to hematological events.
- Renal toxicity was not an important safety concern, with events typically low grade reversible serum creatinine increases. Serious renal events were infrequent and similar between the two treatment arms.
- Lacrimal gland toxicity was not an important safety concern despite the high apparent radiation exposure. Incidences of these toxicities (as evidenced by dry eye and blurred vision) were infrequent and of low grade.
- No patient in either arm had a constellation of values indicative of Hy's law .There was no emerging hepatic safety concern.
- No hematological malignancies or tumors of other exposed tissues were observed.
- Hematology abnormalities were more frequent with ^{177}Lu-PSMA-617 treatment, and usually of higher grade. This was as expected and reflected the similar trend of TEAEs related to myelosuppression.
- There were no clinically significant changes in vital signs or ECGs.
- The safety of ^{177}Lu-PSMA-617 was also evaluated extensively across relevant patient subgroups and no unexpected differences were observed in any of the subgroups and between the two treatment arms.

- Safety topics of interest included AESI for ^{177}Lu-PSMA-617 (Myelosuppression, Fatigue, Dry Mouth, Nausea and Vomiting, and Renal effects); as well as other safety topics considered standard for a comprehensive safety review (Hepatotoxicity, QT Prolongation); and topics considered as potential risks (Second Primary Malignancies, Intracranial Hemorrhage, Reproductive Toxicity). In addition, Lacrimal Toxicity was reviewed. Upon close examination, none of the safety topics raised any specific safety concerns which could translate to a newly identified risk for ^{177}Lu-PSMA-617 treatment.
- There were no potential clinical drug interactions identified for ^{177}Lu-PSMA-617 from the *in vivo* studies conducted.
- There were no new safety concerns in relation to pregnancy or lactation (there are no reports of partner pregnancies), overdose (no cases), drug abuse potential (not foreseen), withdrawal or rebound (no data available), or ability to drive or operate machinery and no element to suggest that the safety profile for ^{177}Lu-PSMA-617 differs from the experiences as documented in literature in similar populations of patients with mCRPC.

In conclusion, ^{177}Lu-PSMA-617 administered intravenously at a dose of 7.4 GBq (200 mCi) once every 6 weeks (±1 week) for a total of 6 cycles based on individual patient safety and tolerability has a well-tolerated and manageable safety profile for the intended use in adult patients with progressive PSMA-positive mCRPC.

8 Appendix

8.1 Published literature

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