CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215833Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	215833
Priority or Standard	Priority
Submit Date(s)	July 29, 2021
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Division/Office	Division of Oncology 1/ Office of Oncologic Diseases
Review Completion Date	*Electronic Stamp Date*
Established Name	^{177}Lu-PSMA-617
(Proposed) Trade Name	Pluvicto
Pharmacologic Class	Radioligand therapeutic agent
Applicant	Advanced Accelerator Applications USA, Inc.
Formulation(s)	Injection solution
Dosing Regimen	Administered once every 6 weeks for a total of 6 doses
Applicant Proposed Indication(s)/Population(s)	treatment of PSMA-expressing metastatic castration-resistant prostate cancer (mCRPC)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

^{68}Ga-PSMA-11	Gallium-labeled PSMA-11
^{177}Lu-PSMA-617	Lutetium-labeled PSMA-617
AAA	Advanced Accelerator Applications
ADME	absorption, distribution, metabolism, and excretion
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APCCC	Advanced Prostate Cancer Consensus Conference
AR	androgen receptor
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATM	ataxia-telangiectasia (A-T) mutated gene
BICR	blinded independent central review
BRA	benefit risk assessment
BRCA	BReast CAncer gene
BLA	Biologics License Applications
BPI-SF	brief pain inventory – short form
BSC/BSoC	best Supportive/Best Standard of Care
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	corona virus disease 19
CR	complete response
CRF	case report form
CRO	contract research organization
CRPC	Castration resistant prostate cancer
CSF	cerebro-spinal fluid
CSR	clinical study report
CT	computed tomography
CL	Clearance
CYP	Cytochrome
DCO	data cut-off

DCR	disease control rate
DDI	drug-drug interaction
DE	Germany
DMC	data monitoring committee
DMF	Drog Master File
DKFZ	Deutsches Krebsforschungszentrum; the German Cancer Research Center
DoR	duration of response
DOTA	Dodecane tetraacetic acid
EBRT	external beam radiation therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EMA	European Medicines Agency
EOT	end of treatment
ESMO	European Society for Medical Oncology
EQ-5D-5L	European Quality of Life (EuroQol) – 5 Domain 5 Level scale
FACT-G	functional assessment of cancer therapy – general
FACT-P	functional assessment of cancer therapy – prostate
FAS	full Analysis Set
FDA	Food and Drug Administration
GB	Great Britain
GCP	good clinical practice
GI	gastro-intestinal
GRMP	good review management practice
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologus recombination repair
IDMC	independent data monitoring committee
IEC	independent ethics committee
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
i.v.	Intravenous
KM	kaplan-meier
LDH	lactate dehydrogenase
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities

MRI	magnetic resonance imaging
mITT	modified intent to treat
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDS	myelodysplastic syndromes
mPC	metastatic prostate cancer
NE	not evaluated
NAAD	Novel androgen axis drug (for example abiraterone or enzalutamide)
NCCN	Nation Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New Drug Application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAP-GM-CSF	pulmonary alveolar proteinosis-granulocyte macrophage colony-stimulating factor
PARP	poly ADP-ribose polymerase
PC	prostate cancer
PCS	Prostate cancer subscale
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PET-CT	positron emission tomography–computed tomography
PFS	progression-free survival
PI	prescribing information
PK	Pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial Response
PREA	Pediatric Research Equity Act
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PSA	prostate-specific antigen
PSADT	PSA doubling time
PSMA	prostate-specific membrane antigen
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumours

REMS	risk evaluation and mitigation strategy
RLT	radioligand therapy
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	standard organ class
SSE	symptomatic skeletal event
TEAE	treatment emergent adverse event
ULN	upper Limit of Normal
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

^{177}Lu-PSMA-617 (PLUVICTO) is a beta-emitting small molecule radioligand therapeutic agent that targets prostate-specific membrane antigen (PSMA)-expressing prostate cancer cells.

The Applicant's proposed indication for the NDA is:

> *PLUVICTO is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) path way inhibition and taxane-based chemotherapy* (b) (4)

FDA's recommended indication is:

> *PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.*

The dosing regimen proposed for 177Lu-PSMA-617 is 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 doses, or until disease progression, or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team has determined that 177Lu-PSMA-617 administered at a dose of 7.4 GBq (200 mCi) intravenously every 6 weeks for up to 6 doses, or until disease progression, or unacceptable toxicity, resulted in a statistically significant and clinically meaningful improvement in overall survival (OS) when combined with best standard of care (BSoC) compared to BSoC alone in a large, adequate, and well-controlled randomized phase III trial evaluating patients with mCRPC.

The evidence to support the proposed indication and provide substantial evidence of effectiveness comes from the ongoing VISION trial, a Phase III, randomized (2:1), open-label, multi-national clinical trial of 177Lu-PSMA-617 + BSoC vs. BSoC alone in patients with MCRPC who have received at least one prior AR inhibitor and one or two taxane regimens. Patients in VISION were selected for treatment by PET-CT scans using gallium (Ga) 68 gozetotide, a radioactive diagnostic agent.

Enrollment criteria for VISION included having a histological, pathological, and/or cytological diagnosis of progressive mCRPC with at least 1 metastatic lesion that is present on baseline CT, MRI, or bone scan Imaging. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver. Randomization was stratified by baseline lactate dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an AR pathway inhibitor as part of BSoC at the time of randomization. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were required to have received at least one AR pathway inhibitor, and 1 or 2 prior taxane-based chemotherapy regimens.

Patients were randomized to receive ^{177}Lu-PSMA-617 plus BSoC (N = 551) or BSoC alone (N = 280). Patients received ^{177}Lu-PSMA-617 at a dose of 7.4 GBq (200 mCi) every 6 weeks for up to a total of 6 doses plus BSoC or BSoC alone. BSoC administered at the investigator's discretion included supportive measures (pain medications, hydrations, etc.), ketoconazole, androgen reducing agents (including any corticosteroid and 5-alpha reductases), newer anti-androgen drugs ([NAAD] abiraterone, enzalutamide, apalutamide, or any other NAAD), radiation in any external beam or seeded form, and bone-targeted agents (zoledronic acid, denosumab, and any bisphosphonates). Combinations of any, and all, of the above were allowed on the study and could be modified over time as needed. Cytototoxic chemotherapy, immunotherapy, other systemic radio isotopes or hemi-body radiotherapy were not allowed as part of BSoC. After 4 cycles of treatment with ^{177}Lu-PSMA-617, patients were assessed for evidence of response, residual disease, and tolerance to therapy. If patients met these criteria, they could receive 2 additional cycles of ^{177}Lu-PSMA-617 at investigator discretion.

The primary endpoints (termed alternative endpoints in protocol) were OS and rPFS by PCWG3 criteria and blinded independent central review (BICR). The primary endpoint of OS met statistical significance with an improvement on the ^{177}Lu-PSMA-617 plus BSoC arm compared to the control arm (HR 0.62 (95% CI: 0.52, 0.74, p<0.001)). Median OS on the ^{177}Lu-PSMA-617 plus BSoC arm (15.3 months) was longer than on the BSC/BSoC arm (11.3 months). The OS result was supported by a statistically significant improvement in rPFS in the ^{177}Lu-PSMA-617 plus BSC/BSoC arm compared to the BSoC arm with a HR 0.40 (95% CI: 0.31, 0.52, p<0.001). The ^{177}Lu-PSMA-617 plus BSC/BSoC had a median rPFS of 8.7 months and for the BSC/BSoC was 3.4 months.

The review team evaluated several issues during the course of the review. The VISION trial had considerable withdrawal of consent and disproportiante dropout in the BSoC only (control) arm. This was attributed to the non-blinded trial design, with patients withdrawing consent when they realized they were assigned to the control arm and not going to receive the

investigational therapy. The Applicant implemented corrective actions during the trial and withdrawal of consent decreased considerably as a result. Subsequently, rPFS was only prospectively analyzed in patients randomized after these measures were implemented (PFS-FAS analysis set). The PFS-FAS analysis set served to mitigate, but not eliminate, asymmetric censoring in the analysis of rPFS because rPFS data could not be collected for the patients with early dropout. The applicant was able to ascertain survival status for many patients who withdrew consent, and OS was analyzed in all randomized patients (FAS analysis set).

The effect of disproportionate drop out in the BSoC arm compared to the investigational arm was evaluated further by the clinical and statistical teams during FDA review. Where feasible, patients could be followed for overall survival via public registries if they dropped out, and this was specified in the site specific informed consent. Thus, asymmetric censoring due to withdrawal of consent was reduced for OS events in the primary analysis (OS FAS analysis set).

Censoring due to withdrawal was reduced but not eliminated, and the effect of asymmetric censoring was further investigated. In the OS FAS analysis, 15 patients (2.7%) were censored due to withdrawal of consent in the ^{177}Lu-PSMA-617 arm compared to 22 patients (11.8%) in the BSoC arm. Several sensitivity analyses conducted by the Applicant demonstrated that the OS benefit was maintained when assessing the impact of censoring due to drop-outs. An extreme case analysis considered all drop-outs in the the ^{177}Lu-PSMA-617 arm as events. Two best case analyses imputed data for drop-outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSoC only arm. A tipping-point analysis quantified the increase or decrease in the risk of events in patients dropping out of the ^{177}Lu-PSMA-617 arm or the BSoC arm that would make the primary analysis lose statistical significance. The results of sensitivity analyses of OS supported the statistically robust finding of superiority for OS results which were felt to be clinically meaningful. Sensitivity analyses of the rPFS results due to early withdrawal were supportive of a statistically superior effect favoring the ^{177}Lu-PSMA-617 arm. However, interpretation of the magnitude of the rPFS effect was limited due to the high degree of censoring from early drop out in the control arm. Additional efficacy results from key secondary endpoints including an ORR of 30% with 6% CR were consistent and supported the efficacy of ^{177}Lu-PSMA-617.

In VISION, patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver; there is insufficient data on efficacy in this population. A post-marketing evaluation will be done by the Applicant to assess the efficacy and safety of ^{177}Lu-PSMA-617 in patients who did not meet criteria for enrollment on VISION.

Safety data for ^{177}Lu-PSMA-617 were obtained from 529 patients with mCRPC in VISION, who received at least one dose of ^{177}Lu-PSMA-617. The most common adverse reactions (≥ 20%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617 were fatigue, dry

mouth, nausea, anemia, decreased appetite, and constipation. The most common laboratory abnormalities that worsened from baseline in ≥ 30% of patients who received ^{177}Lu-PSMA-617 plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium. Two patients had fatal pancytopenia. Two deaths due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia and one death due to sepsis and concurrent neutropenia were observed in patients who received 177Lu-PSMA-617.

Serious adverse reactions occurred in 36% of patients who received ^{177}Lu-PSMA-617. Fatal adverse reactions occurred in 2.8% of patients who received ^{177}Lu-PSMA-617 plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%). ^{177}Lu-PSMA-617 was permanently discontinued due to adverse reactions in 12% of patients. Adverse reactions leading to a dose interruption, dose reduction, and permanent discontinuation of ^{177}Lu-PSMA-617 occurred in 16%, 6%, and 12% of patients, respectively.

The duration of follow up at the time of this review was not adequate to allow for a reliable characterization of potential long-term toxicities in patients receiving the investigational agent. A PMR was issued requiring the Applicant to conduct an integrated safety analysis to further characterize the potential long term toxicities of ^{177}Lu-PSMA-617.

The improvement in OS was considered statistically significant, robust and clinically meaningful. The OS result was felt to outweigh the risk of observed toxicities associated with this therapy. The review team recommends that ^{177}Lu-PSMA-617 be granted regular approval for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

^{177}Lu-PSMA-617 (PLUVICTO) is a beta-emitting small molecule radioligand therapeutic agent that targets prostate-specific membrane antigen (PSMA)-expressing prostate cancer cells.

The efficacy of ^{177}Lu-PSMA-617 was evaluated in VISION (NCT03511664), a randomized (2:1), multicenter, open-label trial that evaluated ^{177}Lu-PSMA-617 plus BSoC (N = 551) or BSoC alone (N = 280) in men with progressive, PSMA-positive mCRPC. Randomization was stratified by baseline lactase dehydrogenase (LDH), presence of liver metastases, ECOG PS score and inclusion of an androgen receptor pathway inhibitor as part of BSoC at the time of randomization. All patients received a GnRH analog or had prior bilateral orchiectomy. Patients were required to have received at least one AR pathway inhibitor, and 1 or 2 prior taxane-based chemotherapy regimens. Eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver.

The alternative primary endpoints were OS and rPFS (by BICR per PCWG3 criteria). Either could be positive to satisfy primary endpoint. The primary endpoint of OS was met, with patients randomized to receive ^{177}Lu-PSMA-617 having prolonged OS (median estimate 15.3 months) compared to BSC/BSoC (median estimate 11.3 months), HR 0.62 (95% CI: 0.52, 0.74, p<0.001).The primary endpoint of BICR assessed rPFS was also met, with patients randomized to receive ^{177}Lu-PSMA-617 plus BSC/BSoC having prolonged rPFS (median estimate 8.7 months) compared to BSC/BSoC (median estimate 3.4 months), HR 0.40 (95% CI: 0.31, 0.52, p<0.001). Key secondary endpoints, including a 30% ORR with median duration of response of 10 months assessed by RECIST v1.1, further supported the efficacy of ^{177}Lu-PSMA-617. Disproportionate dropout in the BSoC arm compared to the ^{177}Lu-PSMA-617 arm was a key review issue and several sensitivity analyses in conjunction with the consistency observed across several other efficacy endpoints supports the demonstrated efficacy of ^{177}Lu-PSMA-617 in VISION. This is discussed further in Section 8 of this review.

The safety profile of ^{177}Lu-PSMA-617 is acceptable in this setting. Fatal adverse reactions occurred in 2.8% of patients who received ^{177}Lu-PSMA-617. Two patients had fatal pancytopenia. Two deaths due to intracranial hemorrhage and subdural hematoma in association with

thrombocytopenia and one death due to sepsis and concurrent neutropenia were observed in patients who received177Lu-PSMA-617. Adverse reactions leading to a dose interruption, dose reduction, and permanent discontinuation of ^{177}Lu-PSMA-617 occurred in 16%, 6%, and 12% of patients, respectively. The most common adverse reactions (≥ 20%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617 plus BSoC were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. The most common laboratory abnormalities that worsened from baseline in ≥ 30% of patients who received ^{177}Lu-PSMA-617 plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

Risk from radiation exposure, myelosuppression, renal toxicity, embryo-fetal toxicity, and infertility are labeled as Warnings and Precautions. Because of relatively short duration of follow up for a radioligand therapeutic drug, longer follow up for better assessment of delayed toxicities of radiation is required.

The review team recommends that ^{177}Lu-PSMA-617 be granted regular approval for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

Table 1: Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Metastatic CPRC is a serious and incurable condition	Patients with mCRPC who have been treated with androgen receptor pathway inhibition (ARPI) and taxane-based chemotherapy have a serious and life-threatening condition with limited treatment options, none of which are curative. Patients with mCRPC whose disease progresses after ARPIs and taxanes have a poor prognosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are several approved drugs with proven OS benefit in patients with mCRPC. However, the optimal sequencing of therapies is unknown and mCRPC remains incurable. • FDA-approved therapies for patients with MCRPC include abiraterone, enzalutamide, radium-223, sipuleucel-T, and olaparib. docetaxel and cabazitaxel are also therapeutic options in these patients. All of these therapies have demonstrated prolonged survival with their use, albeit in patient populations with mCRPC that differ by prior therapies received. • There is a lack of prospective data on therapies that improve survival in patients who have already progressed on taxane chemotherapy and an AR inhibitor.	Patients with mCRPC whose disease progresses after AR inhibitors and taxanes have a limited treatment options. Although treatment options exist, none are curative and none are approved specifically for patients whose disease has progressed after treatment with 2-3 prior lines of therapy. Additionally, some patients may not be medically fit to received some of the available therapies due to risk of severe toxicities. Therefore, there is an unmet medical need for new, effective and tolerable treatments for patients with mCRPC who have received at least 2 prior lines of therapy.
Benefit	The efficacy of ^{177}Lu-PSMA-617 was evaluated in VISION, a randomized (2:1), multicenter, open-label trial that evaluated ^{177}Lu-PSMA-617 plus BSoC (N = 551) or BSoC alone (N = 280) in men with progressive, PSMA-positive mCRPC. • The alternative primary endpoints were rPFS (by BICR per PCWG3 criteria) and OS. Either could be positive to satisfy primary endpoint. The primary endpoint of OS was met, with patients randomized to receive 177Lu-PSMA-617 having prolonged OS (median estimate 15.3 months) compared to BSC/BSoC (median estimate 11.3 months), HR 0.62 (95% CI: 0.52, 0.74, p<0.001). The primary endpoint of BICR assessed rPFS was met, with patients randomized to receive 177Lu-PSMA-617 plus BSC/BSoC having prolonged rPFS	^{177}Lu-PSMA-617 has demonstrated a statistically significant and clinically meaningful improvement in OS supported by rPFS and a durable ORR of 30%.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(median estimate 8.7 months) compared to BSC/BSoC (median estimate 3.4 months), HR 0.40 (95% CI: 0.31, 0.52, p<0.001). • Key sensitivity and subgroup analyses were supportive of the primary efficacy results. Notably, sensitivity analyses considering extreme scenarios and the potential for informative censoring as a result of the disproportionate drop out of patients in VISION supported the primary efficacy findings. • Secondary endpoints, including ORR by RECIST v1.1 and delay in time to first symptomatic skeletal event further supported the efficacy of ^{177}Lu-PSMA-617 in VISION.	
Risk and Risk Management	• The safety profile of ^{177}Lu-PSMA-617 is acceptable in this setting. Fatal adverse reactions occurred in 2.8% of patients who received ^{177}Lu-PSMA-617. Two patients had fatal pancytopenia. Two deaths due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia and one death due to sepsis and concurrent neutropenia were observed in patients who received177Lu-PSMA-617. • Duration of follow up is relatively short for comprehensive assessment of delayed toxicities of ^{177}Lu-PSMA-617. • There is very limited data on safety of ^{177}Lu-PSMA-617 in patients with moderate renal impairment and no data in patients with severe renal impairment.	Extended follow-up for ^{177}Lu-PSMA-617 will be required as a PMR to provide further safety data on the radiation-induced delayed toxicities of ^{177}Lu-PSMA-617. Assessment of safety of ^{177}Lu-PSMA-617 in patients with moderate or severe renal impairment will be required as a PMR to better assess the risk of treatment with ^{177}Lu-PSMA-617 in these patients. No REMS will be required. The safety profile of ^{177}Lu-PSMA-617 is acceptable for the indicated patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include exploratory analyses.			See Section 8 for further details
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		

	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Prostate cancer (PC) is globally the second most common cancer in men and the fifth most common cause of cancer death among men, with an estimated 1.4 million new cases and 375,304 cancer deaths in 2020 worldwide (Sung et al 2021). It is the second leading cause of cancer-related death among men in the USA, and the third leading cause in Europe (Malvezzi et al 2019, Siegel et al 2020). In the USA, approximately 191,930 new cases of PC and 33,330 deaths were estimated for 2020 (ACS 2020), and in Europe, the corresponding estimates were 473,344 new cases and 108,088 deaths (IARC 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. Most patients with PC present with localized disease and undergo initial surgical and/or radiological therapy, with concomitant or subsequent use of Androgen deprivation therapy (ADT).

After an initial response to ADT by chemical and/or surgical castration, most patients with metastatic disease progress to to a hormone insensitive stage of the illness, known as metastatic castration-resistant prostate cancer (mCRPC). 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). However, the 5-year survival rate is 30% for patients who present with metastatic disease (ACS 2020), as the development of castration-resistance is inevitable, resulting in transition to the fatal mCRPC. Once patients reach the mCRPC stage, their expected overall survival is low (9.8 months) (Smith et al 2016).

^{177}Lu-PSMA-617 is a radioligand therapy (RLT) that targets prostate-specific membrane antigen (PSMA)-expressing prostate cancer lesions in a specific manner by exploiting cell surface proteins mainly expressed on malignant cells. PSMA is a promising RLT target because it is highly expressed in PC, including mCRPC, but it has low and restricted expression in normal tissues (Bostwick et al 1998, Sokoloff et al 2000, Chang 2004, Ghosh and Heston 2004). This differential expression provides a mechanism by which targeted therapeutic radiation can be delivered to cancer cells via PSMA while minimizing radiation-related side effects. PSMA-targeted RLT utilizes a radiolabeled small-molecule ligand that targets and binds with high affinity to PSMA, resulting in internalization and retention within the targeted PC cell (Ghosh and Heston 2004, Benešová et al 2015), to treat PSMA-positive mCRPC.

The FDA's Assessment: FDA agrees with the Applicant's analysis of prostate cancer in the metastatic castration-resistant setting.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The current standard of care in metastatic prostate cancer (mPC) is based on chemotherapy, androgen deprivation by different mechanisms of action on the hypothalamic-pituitary-gonadal axis, and adrenal-androgen receptor signaling. Standard ADT and androgen receptor (AR) pathway inhibitors (i.e. abiraterone acetate or enzalutamide) are commonly well tolerated and can stabilize metastatic castration-sensitive PCs (mCSPC) for many years. However, most patients eventually progress to mCRPC, which remains challenging to treat. Available therapies for PC are presented in Table 2.

Several agents have been approved for the treatment of mCRPC. Docetaxel has been approved for patients with mCRPC for over 16 years, and during the past decade additional therapeutic options have been approved, including the taxane-based cytotoxic agent cabazitaxel, sipuleucel-T immunotherapy for asymptomatic or minimally symptomatic disease, the AR pathway inhibitors such as abiraterone acetate and enzalutamide, the α-emitting bone-directed radiotherapy ^{223}Ra dichloride for bone-only metastases, and more recently poly ADP-ribose polymerase (PARP) inhibitors in those with specified homologus recombination repair (HRR) defects. Nation Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and Advanced Prostate Cancer Consensus Conference (APCCC) guidelines provide some consensus and guidance for their use, but there is no agreed sequence for delivery of these agents in patients with mCRPC. In clinical practice, AR pathway inhibitors 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 abiraterone acetate or enzalutamide and for symptomatic patients, particularly with visceral disease. Docetaxel is used more commonly (Flaig et al 2016), and cabazitaxel was specifically designed for antitumor activity in docetaxel-resistant patients (de Wit et al 2019). Because both agents have a typical chemotherapy side-effect profile (including bone marrow suppression), they are often not considered due to multiple comorbidities, poor hematological reserve, or patient refusal (Zielinski et al 2014). When the approved second-line treatments (e.g. abiraterone acetate or enzalutamide) are used in the third-line setting, they do not retain the same levels of activity as when used in second line. AR pathway inhibitors in patients previously exposed to a taxane and either abiraterone acetate or enzalutamide produce only modest activity in terms of prostate-specific antigen (PSA) decline, and progression-free survival (PFS) and overall survival (OS) benefit (Loriot et al 2013, Noonan et al 2013, Azad et al 2015, Brasso et al 2015, Cheng et al 2015). As AR pathway inhibitors have been used in earlier lines of therapy, the use of a second AR inhibitor following docetaxel has resulted in diminished efficacy, likely due to cross resistance.

Despite the broadening therapeutic landscape for mCRPC over the last decade, there are limited options following progression on taxane-based chemotherapy, or when taxane-based chemotherapy is contraindicated in patients, or when patients are not candidates for taxane-based chemotherapy and do not have alternative options (Sartor et al 2018). These

limitations underscore the necessity for improved treatment regimens with a significant antitumor effect and minimal toxicity. Prolonged survival in this patient population is currently an unmet need and novel treatments are still required.

The FDA's Assessment:
FDA agrees with the Applicant's analysis of current treatment options for mCRPC . There are several available therapies for patients with advanced prostate cancer that have demonstrated prolongation of survival in large, randomized clinical trials. Metastatic castration resistant prostate cancer is the final clinical state of prostate cancer (PCWG3) and represents a patient population with an unmet need, as these patients will die of their disease and may also encounter substantial morbidity prior to death. Therapies that can improve quality of life and/or prolong survival are needed.

Table 2 – Summary of Current Therapies in Prostate Cancer

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Androgen-receptor (AR) pathway inhibitors					
Abiraterone Acetate (ZYTIGA)	mCRPC	2011 (post-docetaxel); 2012 (mCRPC taxane-naive)	1000 mg orally once daily with prednisone 5 mg orally once daily	- vs. placebo OS: 15.8 vs. 11.2 months (HR = 0.740; 95% CI: 0.638, 0.859)	Warnings: adrenocortical insufficiency, mineralocorticoid excess, hepatoxicity Common ADRs: fatigue, arthralgia, hot flushes, hypertension, GI
Enzalutamide (XTANDI)	mCRPC	2012 (mCRPC post-docetaxel); 2014 (taxane-naive mCRPC)	160 mg administered orally once daily	- vs. placebo OS: 18.4 vs. 13.6 months (HR = 0.63; 95% CI: 0.53, 0.75, p < 0.0001)	Warnings: seizures, falls and fractures, PRES, ischemic heart disease, embryofetal tox Common ADRs: asthenia, decreased appetite, hot flushes, arthralgia, vertigo, hypertension
Chemotherapeutics					
Docetaxel (TAXOTERE)	mCRPC	2004	75 mg/m2 every 3 weeks iv with 5 mg prednisone orally twice a day continuously	- vs. Mitoxantrone + Prednisone OS: 18.9 vs 16.5 (HR = 0.761; 95% CI 0.619 to 0.936, p = 0.0094)	Warnings: hepatic impairment, hematological effects, hypersensitivity reactions, fluid retention, AML, cutaneous reactions, neurological reactions, eye disorders, asthenia Common ADRs: infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea,

					constipation, anorexia, nail disorders, fluid retntion, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia .
Cabazitaxel (JEVTANA)	mCRPC previously treated with a docetaxel-containing treatment regimen	2010	20 mg/m2 every 3 weeks i.v. with 10 mg prednisone orally once a day continuously	- vs. Mitoxantrone + Prednisone OS: 15.1 vs 12.7 (HR = 0.70; 95% CI 0.59 to 0.83, p = <0.0001) - vs. Abiraterone + Prednisone/Prednisolone or Enzalutamide OS: 13.6 vs 11.0 (HR = 0.64; 95% CI 0.46 to 0.89, p = 0.0078) rPFS: 8.0 vs 3.7 (HR = 0.54; 95% CI 0.40 to 0.73, p = <0.0001) ORR: 36.5% (95%C CI 26.6 to 48.4) vs 11.5% (95% CI 2.9 to 20.2), p = 0.004	Warnings: severe neutropenia, hypersensitivity, GI, renal failure, increased fatal cases in the elderly Common ADRs: neutropenia, anemia, GI, fatigue, asthenia, hematuria, decreased appetite, back pain, abdominal pain
Radiopharmaceutical					
Radium-223 (XOFIGO)	CRPC, symptomatic bone metastases and no know visceral metastatic disease	2013	55 kBq per kg body weight, given at 4 week intervals for 6 injections	- vs. Placebo OS: 14.9 vs 11.3 (HR = 0.695; 95% CI 0.581 to 0.832)	Warnings: bone marrow suppression, increased fractures, embryofetal toxicity Common ADRs: GI, peripheral edema
Immunotherapy					
Sipuleucel-T (PROVENGE)	Asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer	2010	Each dose contains a minimum of 50 million autologous CD54+ cells activated with PAP-	Study 1 vs. control OS: 25.8 vs 21.7 months (HR = 0.775; 95% CI 0.614 to 0.979, p = 0.032)	Warnings: acute infusion reactions Common ADRs: chills, fatigue, fever, back pain, nausea, joint ache, headache

			GM-CSF. The recommended course of therapy is 3 complete doses, given at approximately 2-week intervals.	Study 2 vs control OS: 25.9 vs. 21.4 (HR = 0.586; 95% CI 0.388 to 0.884, p = 0.010)	
PARP Inhibitors					
Rucaparib (RUBRACA)*	BRCA-associated mCRPC – who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy	2020	600 mg taken orally twice daily for a total daily dose of 1,200 mg	Confirmed ORR = 44% (95% CI 31 to 57); Median DOR NE (95% CI 6.4 to NE)	Warnings: MDS/AML, embryofetal toxicity Common ADRs: asthenia, anemia, GI, liver enzymes increased, thrombocytopenia, rash
Olaparib (LYNPARZA)	HRR gene-mutated mCRPC who have progressed following prior treatment with enzalutamide or abiraterone	2020	300 mg taken orally twice daily; patients should also receive a gonadotropin-release hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.	Cohort A (BRCA1, BRCA2 or ATM mutations) vs Enzalutamide or Abiraterone: rPFS: 7.4 vs 3.6 months (HR = 0.34; 95% CI 0.25 to 0.47, p = <0.0001) Confirmed ORR: 28% vs 1% (p <0.0001) OS: 19.2 vs 14.7 (HR = 0.69; 95% CI 0.5 to 0.97, p = 0.0175 Cohort A+B (mutations among 12 other genes involved in the HRR pathway) rPFS: 5.8 vs 3.5 (HR = 0.49; 95% CI 0.38 to 0.63, p < 0.0001)	Warnings: MDS/AML, pneumonitis, embryo-fetal toxicity, venouse thromboembolic events Common ADRs: nausea, fatigue (including asthenia), anemia, vomiting, diarrhea, decreased appetite, headache, neutropenia, dysgeusia, cough, dyspnea, dizziness, dyspepsia, leukopenia, thrombocytopenia, and abdominal pain upper
Source Drugs@FDA *Accelerated approval					

The FDA's Assessment:
FDA agrees with the Sponsor's summary of available therapies for mCRPC. Note that Table 2 summarizes the available treatment options only for metastatic CRPC, and does not include other therapies that patients may have received in other/earlier disease settings (e.g., metastatic hormone sensitive prostate cancer or non-metastatic CRPC).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Lutetium (^{177}Lu) vipivotide tetraxetan (AAA617/[^{177}Lu]Lu-PSMA-617) is not currently registered (or approved) in the US or in any other part of the world.

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

The FDA's Assessment:
FDA agrees with the Applicant's position on U.S. regulatory actions and marketing history of ^{177}Lu-PSMA-617.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
^{177}Lu-PSMA-617 was initially developed by the German Cancer Research Center, Deutsches Krebsforschungszentrum (DKFZ) in collaboration with University Hospital Heidelberg (Kratochwil et al 2015). Following initial non-clinical development of ^{177}Lu-PSMA-617, the compound was licensed to ABX GmbH in Germany. On 02 October 2017, Endocyte, Inc. announced the completion of an exclusive worldwide license of the cold peptide PSMA-617 from ABX GmbH. With the license agreement Endocyte, Inc. assumed responsibility for global development of ^{177}Lu-PSMA-617 and initiated the Phase III VISION study (PSMA-617-01: An International, Prospective, Open-label, Multicenter, Randomized Phase III Study of ^{177}Lu-PSMA-617 in the Treatment of Patients with Progressive PSMA-positive Metastatic Castration-resistant Prostate Cancer (mCRPC), EudraCT No.: 2018-000459-41, NCT03511664) to support

regulatory submission and approval. Table 3 summarizes the key FDA interactions the Sponsor had after licensing ^{177}Lu-PSMA-617.

Table 3: Key FDA Interactions

Type of meeting	Date	Purpose of meeting
FDA Type B End of Phase II Meeting	30-Jan-2018	To seek guidance on the proposed development of ^{177}Lu-PSMA-617 for mCRPC in patients expressing PSMA, who have already received abiraterone and/or enzalutamide and at least one prior taxane-containing regimen. The Sponsor's inquiry focused on the Phase III study, overall clinical and nonclinical plans for this therapeutic agent, as well as the proposed development plan of the radioactive diagnostic agent ^{68}Ga-PSMA-11, with intention to support registration.
FDA Type B End of Phase II Meeting	16-Aug-2018	To request feedback regarding the potential for an expedited path to submission based on data from Phase III Study PSMA-617-01. To seek feedback on using rPFS to support a NDA, assuming positive data from Study PSMA-617-01.
FDA Type B CMC End of Phase II, written response only Meeting	20-Dec-2018	To discuss the proposed CMC development plan in support of a future NDA.
FDA Type A Meeting	02-May-2019	To obtain guidance on the operational, statistical, and design-related actions to mitigate the challenges caused by a high number of subjects withdrawing consent from the control arm of Study PSMA-617-01. To discuss the proposed approach to ensure a meaningful comparison between the randomized treatment arms for rPFS and OS.
FDA Type C Meeting, written response only	24-Mar-2020	To obtain agreement on the overall organization and layout of the content that will be included in the NDA for ^{177}Lu-PSMA-617
FDA Pre-NDA Meeting	02-June-2021	To obtain agreement on the clinical data package and overall content and structure of the planned NDA submission package for ^{177}Lu-PSMA-617.
FDA Type A Written Response Only Meeting	11-June-2021	To confirm the appropriateness of the 505(b)(1) regulatory pathway.

The FDA's Assessment:

FDA agrees with Applicant's summary of key interactions between the FDA and Applicant for evaluation and marketing of ^{177}Lu-PSMA-617 in U.S..

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical data from a randomized trial (Protocol PSMA-617-01 [VISION]) were submitted to the FDA in support of a New Drug Application (NDA) for lutetium (177Lu) vipivotide tetraxetan for use in patients with previously treated, PSMA-expressing mCRPC. Four clinical investigators (CI), Drs. Michael Morris (Site 100104), Nitin Vaishampayan (Site 100029), Scott Tagawa (Site 100152), and Edward Gelmann (Site 100006) and the sponsor (Endocyte, Inc., A Novartis Company) were selected for Good Clinical Practice (GCP) inspections.

Inspections of the four CIs and the study sponsor found no significant regulatory deficiencies. The Applicant's submitted clinical data, including the reported subject PSMA eligibility per the sponsor's prespecified criteria and determination, were verifiable against source records at the sites. Based on the results of these inspections, Study PSMA-617-01 appears to have been conducted adequately, and the clinical data generated by these four CI sites appear reliable and acceptable for this NDA.

4.2. Product Quality

Refer to separate Product Quality review.

4.3. Clinical Microbiology

Refer to separate Clinical Microbiology review.

4.4. Devices and Companion Diagnostic Issues

In VISION, eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs $\geq$ 1 cm, lymph nodes $\geq$ 2.5 cm, bones (soft tissue component) $\geq$ 1 cm] had uptake less than or equal to uptake in normal liver.

Premarket approval application NDA 215841 for ^{68}Ga PSMA-11 for use with PET-CT to select patients for treatment with 177-Lu vipivotide tetraxetan was submitted to CDER for the following indication:

^{68}Ga PSMA-11 is a radioactive diagnostic agent indicated for positron emission tomography

(PET) of PSMA-positive lesions in men with prostate cancer, for selection of patients with metastatic prostate cancer, for whom Lu 17 vipivotide tetraxetan PSMA-directed therapy is indicated.

^{68}Ga PSMA-11 a radioactive diagnostic agent for PET of PSMA-positive lesions, is required to select patients with metastatic prostate cancer for whom lutetium (Lu) 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Please refer to the Division of Imaging and Radiologic Medicine (DIRM) review for further information, filed under NDA 215841.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

Lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto, [^{177}Lu]Lu-PSMA-617 or ^{177}Lu-PSMA-617) is a radiopharmaceutical with radionuclide lutetium-177 linked to a peptide moiety targeting prostate-specific membrane antigen (PSMA). In this NDA, the Applicant submitted study reports of nonclinical pharmacology, pharmacokinetics, and toxicology studies to support the approval of ^{177}Lu-PSMA-617 for treatment of patients with PSMA-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

The active moiety of ^{177}Lu-PSMA-617 is the radionuclide ^{177}Lu which is linked to a peptide ligand that binds to PSMA, a transmembrane protein that is expressed in prostate cancer. ^{177}Lu-PSMA-617 showed nanomolar range binding to PSMA-positive (PSMA[+]) cells in an in vitro pharmacology study, consistent with the study results from cited literature. Upon binding of ^{177}Lu-PSMA-617 to PSMA-expressing cells, the beta-minus emission from ^{177}Lu delivers radiation to PSMA-expressing and surrounding cells and induces DNA damage which can lead to cell death. Research literature showed uptake and internalization of ^{177}Lu-PSMA-617 into PSMA[+] tumor cells and ^{177}Lu-PSMA-617-induced cytotoxicity in vitro in PSMA[+] cells. In published literature, ^{177}Lu-PSMA-617 also showed anti-tumor activity in vivo in mice bearing subcutaneous RM1-hPSMA xenografts with evidence of decreases in tumor volume and increases in overall survival along with tumor uptake of ^{177}Lu-PSMA-617 and DNA double-strand breaks in tumor samples. Secondary pharmacodynamic study results indicated that unlabeled PSMA-617 or non-radioactive ^{175}Lu-PSMA-617 did not have significant interaction with any non-PSMA targets tested and had no cytotoxic effect on PSMA[+] and PSMA[-] cells. Altogether, the pharmacology study results suggested that ^{177}Lu-PSMA-617 delivers radiation to cancer cells via its binding to PSMA-expressing cancer cells, resulting in subsequent cell death by beta emission from ^{177}Lu. The proposed Established Pharmacologic Class (EPC) of "radioligand therapeutic agent" is both clinically relevant and scientifically valid based on the pharmacology study results.

The ligand-mediated toxicities of ^{177}Lu-PSMA-617 were assessed in single-dose toxicity studies in rats and minipigs using a 1:1 mixture of non-radioactive ^{175}Lu-PSMA-617 and unlabeled PSMA-617 and a repeat-dose toxicity study in male rats with weekly administration of unlabeled PSMA-617 for 4 weeks. Toxicology studies were conducted using intravenous (IV) administration, same as the clinical route of administration, and the pivotal studies were conducted in compliance with Good Laboratory Practice regulations (21 CFR part 58). The single- and repeat-dose toxicology studies are considered sufficient for an intended clinical dosing schedule of once every 6 weeks. Single dose IV administration of ^{175}Lu-PSMA-617 and unlabeled PSMA-617 caused no toxicologic

effects in rats at doses up to 4 mg/kg. In minipigs, all doses resulted in acute inflammation at the injection site with associated vascular and perivascular necrosis and hemorrhage on Day 2. After 14 days, minimal or mild vascular/perivascular necrosis was still present with recovery trends. At the high dose, systemic exposures (AUC) of total PSMA-617 (unlabeled PSMA-617 and ^{175}Lu PSMA-617) were 10550 ng*h/mL in rats and 14975 ng*h/mL in minipigs, which corresponds to approximately (b) (4) times and (b) (4) times, respectively, the exposure of ^{177}Lu-PSMA-617 in patients at the recommended mass dose of (b) (4) µg. In the repeat-dose toxicity study in male rats, no adverse treatment-related effects were observed with unlabeled PSMA-617 at doses up to (b) (4) mg/kg. TK evaluation was not included in the study. The high dose of (b) (4) mg/kg ((b) (4) mg/m^2 human equivalent dose [HED]) was approximately (b) (4)-fold higher than the recommended dose of (b) (4) µg or (b) (4) mg/m^2 based on body surface area (BSA) scaling.

Non-radioactive ^{175}Lu-PSMA-617 and unlabeled PSMA-617 did not have adverse effects on the cardiovascular system, respiration, or neurological behavior in safety pharmacology studies in rats or minipigs at mass doses of (b) (4) or (b) (4)-fold higher than the recommended PSMA-617 mass dose of (b) (4) µg in patients based on BSA scaling, respectively.

No systemic toxicities were observed in general toxicology studies in rats and minipigs with a single IV dose of ^{175}Lu-PSMA-617 and unlabeled PSMA-617 at AUC over (b) (4) times of that in human or in rats with repeat doses of unlabeled PSMA-617 at doses up to (b) (4)-fold higher than the human recommended dose based on BSA scaling. The toxicities of ^{177}Lu-PSMA-617 are expected to be associated with the risk of radiation exposure and involve the organs and tissues expressing PSMA. The safety of ^{177}Lu-PSMA-617 was further evaluated in a biodistribution and dosimetry study in rats. The dosimetry study in rats revealed radioactivity in the kidneys after intravenous administration of ^{177}Lu-PSMA-617, and the radiolabeled drug exhibited major clearance through a renal pathway. ^{177}Lu-PSMA-617 radioactivity also accumulated in the blood after a single IV injection, although ^{177}Lu-PSMA-617 was completely cleared from blood 1 day after administration, and there was no distribution of ^{177}Lu-PSMA-617 into erythrocytes in vitro. Based on the study results from the dosimetry study in rats, renal and hematological toxicities are expected with treatment of ^{177}Lu-PSMA-617. In published literature, there was transient ^{177}Lu-PSMA-617 accumulation in the muscle, skeleton, intestine, and liver in rats, and the radioactivity uptake in these organs, except skeleton, gradually decreased over the course of the 7-day study (Das et al 2016, cited by the Applicant). Myelosuppression, GI, renal and liver toxicities were noted in patients treated with ^{177}Lu-PSMA-617. The results of the tissue distribution study suggested that ^{177}Lu-PSMA-617 did not distribute to CNS tissues in rats. Nervous system disorders were observed in patients treated with ^{177}Lu-PSMA-617.

Genotoxicity studies have not been conducted with ^{177}Lu-PSMA-617. As a radioactive product, ^{177}Lu-PSMA-617 is considered genotoxic. Unlabeled PSMA-617 was not mutagenic based on the results from an in vitro bacterial reverse mutation assay.

No reproductive and developmental toxicity studies have been conducted with ^{177}Lu-PSMA-617, PSMA-617, or non-radioactive ^{175}Lu-PSMA-617. ^{177}Lu-PSMA-617 is a genotoxic drug and indicated for advanced prostate cancer. Consistent with ICH S9, reproductive toxicology studies are not warranted to support marketing. The risk of radiopharmaceuticals to a developing fetus is well-established in the scientific literature. Based on its mechanism of action, ^{177}Lu-PSMA-617 can cause fetal harm. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 14 weeks after the last dose. The Applicant's proposed 14-week contraception period after the last dose was calculated using 5 effective half-lives of 177Lu-PSMA-617 ($T_{1/2}$ = 41.6 h) and an additional 3 months. This is consistent with current recommendations in the FDA guidance for industry "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations" for a genotoxic pharmaceutical.

No dedicated fertility studies in animals were conducted or needed given the advanced cancer population and known risk of radiation exposure to human fertility. The clinical team recommended including infertility in the Warnings and Precautions section of labeling given that a radiation absorbed dose to the testis at the recommended dose of 177Lu-PSMA-617 is within the range of causing temporary or permanent infertility.

Radiation is a carcinogen, so carcinogenicity studies are not warranted with the radiopharmaceutical or the cold pharmaceutical. Carcinogenicity studies are also not needed to support a marketing application for a drug intended to treat advanced cancer.

Recommendation
The nonclinical data submitted in this NDA are adequate to support approval of Pluvicto for the treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
There are no referenced NDAs, BLAs or DMFs related to nonclinical pharmacology or toxicology.

5.3. Pharmacology

Primary pharmacology

The FDA's Assessment:

The Applicant submitted the study results from a conducted pharmacology study and cited research data from scientific literature to support the primary pharmacology of ^{177}Lu-PSMA-617. The presented information from literature cited by the Applicant is for scientific discussion on underlining mechanism of action of ^{177}Lu-PSMA-617, and the information is not used for labeling recommendations.

Binding affinity
The binding affinity of ^{177}Lu-PSMA-617 was assessed in cell binding assays using PSMA[+] prostate carcinoma cell line LNCaP C4-2 (ULM-AAA-01-17 Report). The cell binding assays evaluated the competitive binding of ^{177}Lu-PSMA-617 to PSMA on LNCaP C4-2 cells with a serial dilution of unlabeled PSMA-617. ^{177}Lu-PSMA-617 bound to PSMA expressing cells with a Kd value of 4.7 nM and IC_{50} values ranging from 7.7 nM to 13.8 nM in 3 separate experiments. Similar results were shown in cited literature [Benešová et al. 2015], revealing sub-nanomolar binding affinity of PSMA-617 to recombinant human PSMA with an equilibrium dissociation constant (Ki) of 0.4 nM in the enzyme based NAALADase assay, and nanomolar binding affinity to PSMA on LNCaP cells with a Ki of 2.34 nM in a cell-based competitive assay.

In vitro cell uptake and internalization and in vivo tumor uptake
Cell uptake and internalization were investigated with ^{177}Lu-PSMA-617 using PSMA[+] PC-3 PIP and PSMA[-] PC-3 flu human prostate cancer cell lines [Umbricht et al. 2017]. After cells were incubated with ^{177}Lu-PSMA-617 for 2 and 4 hours, the total uptake of ^{177}Lu-PSMA-617 was determined by measuring the cell surface bound PSMA fraction and internalized fraction. The total uptake of ^{177}Lu-PSMA-617 into PSMA[+] PC-3 PIP cells was approximately 55% to 70%, whereas the internalized fraction was about 10% to 15% of total added activity. The uptake of ^{177}Lu-PSMA-617 was <0.5% in PSMA[-] PC-3 flu cells.

The tissue distribution profile of ^{177}Lu-PSMA-617 was characterized in PSMA[+] PC-3 PIP and PSMA[-] PC-3 flu tumor-bearing mice [Umbricht et al. 2017]. Mice were sacrificed at different time points post injection of ^{177}Lu-PSMA-617. Radioactivities in selected tissues and organs were measured using a γ-counter. The study results indicated that the uptake of ^{177}Lu-PSMA-617 in PSMA-positive PC-3 PIP tumors was about 32% of the injected activity (IA) per gram of tissue mass (% IA/g) at 15 minutes after injection and increased further to reach a maximum uptake of 56% IA/g after 4 hours. The accumulated activity was below the blood level in PSMA-negative PC-3 flu tumor xenografts.

In vitro and i*n vivo activity*
The effect of ^{177}Lu-PSMA-617 on cell viability (MTTassay) and survival (clonogenic assay) in vitro were examined in PSMA[+] PC-3 PIP and PSMA[-] PC-3 flu cells [Muller et al. 2019]. ^{177}Lu-PSMA-617 reduced viability of PSMA[+] PC-3 PIP tumor cells. The reduction of cell viability in PC-3 PIP tumor cells correlated with the applied radioactivity with more than 90% reduction of cell

survival at a radioactivity level of 10 MBq/mL. In contrast, the viability and survival of PSMA[-] PC-3 flu cells were not altered at radioactivity levels up to 20 MBq/mL and 10 MBq/mL, respectively.

In vivo activity of ^{177}Lu-PSMA-617 was evaluated in a syngeneic model of murine prostate cancer by utilizing mice bearing subcutaneous RM1-hPSMA (RM1 cells stably transduced with human PSMA and SFG-Egfp/Luc) xenografts [Fendler et al. 2017]. RM1 is a murine reconstituted, oncogene-driven prostate cancer cell line. Mice received ^{177}Lu-PSMA-617 by a tail vein injection of either vehicle or 30, 60, 120 MBq total activity of ^{177}Lu-PSMA-617. Anti-tumor activity was assessed by serial CT tumor volumetry and 18F-FDG PET metabolic volume. DNA double-strand breaks in tumor sections were measured by immunohistochemistry using anti-γH2A.X (phospho S139). ^{177}Lu-PSMA-617 induced dose-dependent tumor growth inhibition (↓up to 85% compared to the control on Day 12) with improved survival, which was statistically significant in the 120 MBq dose group compared with other groups. The observed dose-dependent tumor growth inhibition correlated with increases in tumor uptake of ^{177}Lu-PSMA-617 and tumor-to-organ uptake ratios. Administration of ^{177}Lu-PSMA-617 at activities ≥ 60 MBq induced significant DNA damage (≥ 5% positive cells).

Secondary Pharmacology

The Applicant's Position:

^{177}Lu-PSMA-617 binds with high affinity to PSMA for the purpose of delivering therapeutic radiation to prostate cancer cells. The potential for interaction with other targets (receptors, ion channels, enzymes and transporters) was assessed using non-radioactive ^{175}Lu-PSMA-617 at a concentration of 10 µM. This concentration is approximately 132-fold higher than the theoretical clinical Cmax for total peptide exposure (~76 nM) in patients following an administration of ^{177}Lu-PSMA-617. ^{175}Lu-PSMA-617 was tested in binding, enzyme and uptake assays against 87 different targets selected on the basis of their clinical relevance in humans for the evaluation of off-target effects. Results showed ^{175}Lu-PSMA-617 did not have affinity to the receptors in the panel tested since the inhibition of the binding of the natural ligands or of control enzyme activity was less than the significance threshold of 50% in all of the conducted assays.

The mechanism of action of ^{177}Lu-PSMA-617 occurs via PSMA-dependent targeting of the Lutetium-177 radionuclide to targeted cells. In vitro studies showed that non-radioactive ^{175}Lu-PSMA-617 and the unlabeled PSMA-617 precursor did not show any cytotoxic activity on PSMA[+] and PSMA[-]cell lines, even at concentrations of up to 10 µM. This result provides evidence that PSMA-617 and ^{175}Lu-PSMA-617 exert no Lutetium-177-independent cytotoxic pharmacological effect in PSMA[+] or PSMA[-] cells.

The FDA's Assessment:

FDA generally agrees with the assay results summarized by the Applicant. (b) (4) (b) (4) (b) (4) Based on the submitted pharmacology data, ^{177}Lu-PSMA-617 had a nanomolar range binding affinity to PSMA on LNCaP cells.

Safety Pharmacology

The Applicant's Position:

Safety pharmacology studies conducted with PSMA-617 and ^{175}Lu-PSMA-617 demonstrated no effects on CNS or respiratory function in rats, and no effects on cardiac electrophysiological function or hemodynamics as measured by telemetry in conscious minipigs.
In the hERG patch clamp assay, the ^{175}Lu-PSMA-617 test solution induced inhibition of hERG tail current of 8±4%, 8±0% and 13±2%, at 10^{-6}, 10^{-5} and 10^{-4} M concentrations, respectively. The mean maximum inhibition was greater than 10% and less than 30%, nevertheless, since the slope of linear regression was not different from zero, i.e. null slope, the test item was considered to not have an effect on hERG tail current. The negative results in this assay, even at concentrations >1000-fold higher than the theoretical clinical Cmax, further support the lack of a predicted effect on hERG in the clinical setting.

In the in vivo safety pharmacology studies conducted with PSMA-617 and 175Lu-PSMA-617, no significant effects were observed on CNS or respiratory function in rats, and no significant effects were observed on cardiac electrophysiological function or hemodynamics as measured by telemetry in conscious minipigs. Based on body surface area scaling, the safety margin for the central nervous and respiratory systems in rats at the highest dose tested (1.8 mg/kg), is approximately (b) (4)-fold relative to a maximum PSMA-617 mass dose of (b) (4) µg in an average (b) (4) m2 patient. With regard to the cardiovascular system in minipigs, the top dose of (b) (4) mg/kg is equivalent to an estimated safety margin of approximately (b) (4)-fold based on body surface area scaling to the maximum PSMA-617 mass dose of (b) (4) µg in an average (b) (4) m2 patient. Additionally, in rat and minipig toxicology studies conducted with PSMA-617 and 175Lu-PSMA-617, there were no toxicologic effects observed on the CNS, respiratory, or cardiovascular systems.

The FDA's Assessment:

The FDA agrees that there were no adverse effects of PSMA-617 and ^{175}Lu-PSMA-617 on the cardiovascular, respiratory, and central nervous systems in animals in the safety pharmacology core battery. Noteworthy study methods are presented below.

- The test articles used in the in vitro and in vivo studies were a 1:1 mixture of ^{175}Lu-PSMA-617 and PSMA-617.

- Rats:

Rats were given a single intravenous administration of vehicle or test articles at 0.2, 0.6 and 1.8 mg/kg.

Neurological assessment: Behavioral, neurologic or autonomic parameters were evaluated at 5, 15, 30, 60, 120 minutes and 24 hours after dosing, and daily for 6 consecutive days afterwards.

Respiratory assessment: Inspiratory time, expiratory time, peak inspiratory flow, peak expiratory flow, tidal volume, relaxation time, minute volume, respiratory rate and enhanced pause were continuously recorded from at least 30 minutes before dosing up to 3 hours after dosing.

- Minipigs

Minipigs were given an intravenous administration of vehicle or one of the three doses of test articles (0.1, 0.33 and 1.0 mg/kg) with a 7-day interval.

Cardiovascular Assessment: Systolic, diastolic and mean arterial blood pressure, heart rate and Lead II ECG were continuously monitored from 1 hour before, and 5, 15, 30 minutes and 1, 2, 4, 8 and 24 hours after each dosing.

5.4. ADME/PK

The Applicant's Position:

^{177}Lu-PSMA-617 is administered intravenously, therefore no absorption studies were conducted. Following intravenous (i.v.) bolus administration in rats and minipigs, ^{175}Lu-PSMA-617 and PSMA-617 both showed half-lives of approximately 20 min in rats and 1 hour in minipigs and the volume of distribution for both analytes indicated a low distribution into tissues compared to the total body water. ^{175}Lu-PSMA-617 and PSMA-617 were both moderately bound (~50-70%) to plasma proteins in all species evaluated. Blood-to-plasma ratios indicated that PSMA-617 and ^{175}Lu-PSMA-617 are not majorly distributed into erythrocytes. Additionally, ^{175}Lu-PSMA-617 and PSMA-617 were both stable in plasma from human, rat, and minipig for up to 2 hours at 37°C. ^{175}Lu-PSMA-617 and PSMA-617 were also found to be metabolically stable against enzymatic degradation by liver and kidney S9 fractions from human, rat, and minipig. In mice and rats, the distribution of ^{177}Lu-PSMA-617 in most tissues was limited, or transient. Uptake was observed in the PSMA-positive kidneys, however accumulation was found to decrease over time. The elimination of ^{177}Lu-PSMA-617 in rats and mice showed rapid elimination via the renal system into the urine. In rats, more than 95% of the injected dose was eliminated in the urine after 1 day.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the study results. Additional noteworthy results and comments on Applicant's summary are presented in table below.

Table 4. FDA Summary of Major ADME/PK Findings (Data presented by FDA)

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>In vitro plasma protein binding</td><td>
• ^{175}Lu-PSMA-617 and PSMA-617 have similar plasma binding in human, rats and minipigs, with the highest binding in human plasma at 70%;
<table>
<tr><td></td><td colspan="3">In vitro plasma protein binding (% Bound)</td></tr>
<tr><td>Species</td><td>rat</td><td>minipig</td><td>human</td></tr>
<tr><td>^{175}Lu-PSMA-617</td><td>60</td><td>63</td><td>70</td></tr>
<tr><td>PSMA-617</td><td>59</td><td>58</td><td>70</td></tr>
</table>
Note: % Bound at a test concentration of 1 µg/mL is shown in the table. % Bound at a test concentration of 5 µg/mL is lower with the highest binding in human plasma at 58%.

• The blood-to-plasma ratios were less than 1 in mice, rats and minipigs and human, suggesting that PSMA-617 and ^{175}Lu-PSMA-617 are not distributed into erythrocytes.
<table>
<tr><td></td><td colspan="4">Mean blood-to-plasma ratios</td></tr>
<tr><td>Species</td><td>mouse</td><td>rat</td><td>minipig</td><td>human</td></tr>
<tr><td>^{175}Lu-PSMA-617</td><td>0.34</td><td>0.45</td><td>0.55</td><td>0.49</td></tr>
<tr><td>PSMA-617</td><td>0.4</td><td>0.35</td><td>0.42</td><td>0.28</td></tr>
</table>
</td></tr>
<tr><td>Tissue distribution
Mouse

Rat
Study report: ^{177}Lu-PSMA-617-ABX-Biodis-rat</td><td>
No studies were conducted.
The Applicant's presented information on tissue distribution of ^{177}Lu-PSMA-617 in mice was from cited literature [Umbricht et al 2017] and not reviewed.

The biodistribution of ^{177}Lu-PSMA-617 was studied in healthy male rats at 5 minutes, 1 hour, 4 hours, 1 day, 7 days and 14 days after a single intravenous injection of ~1.3 MBq (~36.4 µCi) ^{177}Lu-PSMA-617 per animal (200 kBq/kg) containing 0.21 µg, 2.1 µg, 21 µg non-radiolabeled PSMA-617 (1.1, 9.8, 109.3 µg/kg, respectively).

^{177}Lu-PSMA-617 only accumulated in the kidneys, with the highest activity at 1 h after injection;
After one day, there were only 0.4 % injection dose (ID) of ^{177}Lu-PSMA-617 in the kidneys, and more than 97 % ID were found in the urine;

</td></tr>
</table>

- The uptake of ^{177}Lu-PSMA-617 in the kidney decreased with increasing doses of co-injected non-radiolabeled PSMA-617 peptide;
- No accumulation of ^{177}Lu -PSMA-617 was detected in the muscle, skeleton, intestine, and liver;

Note: Based on published literature (Das et al 2016, cited by the Applicant), there was transient ^{177}Lu-PSMA-617 accumulation in the muscle, skeleton, intestine, and liver in rats, and the radioactivity uptake in these organs, except skeleton, gradually decreased over the course of the 7-day study.

- The radioactivity in the brain represented only the blood volume (approximately 6% v/v) of the brain indicating that ^{177}Lu-PSMA-617 was not distributed to CNS tissues.

Excretion

The evaluation was included in the biodistribution study in rats (see above tissue distribution)

1) There were no differences in the blood clearance with different doses of non-radiolabeled PSMA-617 peptide co-injected with ^{177}Lu-PSMA-617;
2) The half-life of the ^{177}Lu-PSMA-617 in blood was 0.5 h;
3) More than 95 %ID was eliminated in the urine 1-day post-injection, independent of the co-injected peptide amounts;
4) ^{177}Lu-PSMA-617 was almost totally cleared from the organism one week after injection.

TK from general toxicology studies

Rat
Single dose, IV, 2 and 4 mg/kg a 1:1 mixture of ^{175}Lu PSMA-617 and unlabeled PSMA-617

Systemic exposure in rats (combined sexes)

Dose (mg/kg)	Item measured	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng*h/mL)	AUC multiples#
2	^{175}Lu-PSMA-617	6079	3022	up to 202x
	PSMA-617	4830	2267	
4	^{175}Lu-PSMA-617	11411	5817	
	PSMA-617	9984	4733	

#:The exposure multiples were calculated by comparing the exposure of total PSMA-617 of 10550 ng*h/mL (unlabeled PSMA-617 and ^{175}Lu PSMA-617) in rats to human exposure of ^{177}Lu-PSMA-617 at the recommended dose with mean AUC_{Clast} of 52.3 ng.h/mL.

- ^{175}Lu-PSMA-617 and PSMA-617 showed a similar toxicokinetic profile
- $T_{1/2}$ was around 18 min
- Dose-proportional ↑ C_{max} and AUC
- ^{175}Lu-PSMA-617 and PSMA-617 were mainly distributed in the circulating blood, suggested by the distribution volume;
- No gender differences.

Minipig
Single dose, IV,

Systemic exposure in minipigs (combined sexes)

Dose (mg/kg)	Item measured	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng*h/mL)	AUC multiples#

<table>
<tr><td rowspan="5">0.2, 0.6 and 1.8 mg/kg
a 1:1 mixture of ^{175}Lu PSMA-617 and unlabeled PSMA-617</td><td rowspan="2">0.2</td><td>^{175}Lu-PSMA-617</td><td>445</td><td>387</td><td rowspan="4">up to 286x</td></tr>
<tr><td>PSMA-617</td><td>693</td><td>709</td></tr>
<tr><td rowspan="2">1.8</td><td>^{175}Lu-PSMA-617</td><td>5829</td><td>5372</td></tr>
<tr><td>PSMA-617</td><td>10092</td><td>9603</td></tr>
<tr><td colspan="5">#:Exposure multiples were calculated by comparing the exposure of total PSMA-617 of 14975 ng*h/mL (unlabeled PSMA-617 and ^{175}Lu PSMA-617) in minipigs to human exposure of ^{177}Lu-PSMA-617 at the recommended dose with mean AUC_{Clast} of 52.3 ng.h/mL.
• ^{175}Lu-PSMA-617 and PSMA-617 showed a similar toxicokinetic profile
• $T_{1/2}$ was around 1-1.2 hour
• > Dose-proportional ↑C_{max} and AUC
• ^{175}Lu-PSMA-617 and PSMA-617 were mainly distributed in the circulating blood, suggested by the distribution volume;
• Exposure in males was slightly less than that in females (0.77-1x).</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

The FDA's Position: (Data presented by FDA):

Study title/ number: ^{175}Lu-PSMA-617 solution- Single dose intravenous extended toxicity study in rats/ A3732

- No adverse effects were observed in rats given a single intravenous injection of ^{175}Lu-PSMA-617 with PSMA-617 at 2 and 4 mg/kg;
- A similar TK profile was observed for ^{175}Lu-PSMA-617 and PSMA-617.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	2, 4 mg/kg*, 5 mL/kg, single dose [a 1: 1 mixture of ^{175}Lu PSMA-617 and unlabeled PSMA-617] *dose of total PSMA-617 (unlabeled PSMA-617 and ^{175}Lu PSMA-617)
Justification of doses:	Not provided
Route of administration:	intravenous bolus injection
Number/Sex/Group:	15/sex/group (main), 9/sex/group (TK, 3/sex for control)
Scheduled terminate	Day 2 (10/sex/group); Day 15 (5/sex/group)
Formulation/Vehicle:	Injection solution/low metal content water (EMSURE® water for analysis (Merck KGaA Product No. 1.16754))
Species/Strain:	Rat
Age:	27-29 days old
Deviation from study protocol affecting interpretation of results:	No
Comment on Study Design and Conduct:	none

Table 5. Toxicology observations and results in rats/ A3732

Parameters	Major findings
Mortality	None
Clinical Signs	unremarkable
Body weight	unremarkable
Food consumption	unremarkable
Hematology	Changes compared to the control Day 2: -↑Monocytes in females at 4 mg/kg (↑50%), statistically significant Day 15: -↑Eosinophils in males at 4 mg/kg (↑72%)
Clinical chemistry	unremarkable
Urinalysis	unremarkable
Gross Pathology	unremarkable
Organ Weights	unremarkable
Histopathology **Adequate battery: Yes**	unremarkable

Toxicokinetics	Refer to ADME/PK section

Study title/ number: ^{175}Lu-PSMA-617 solution- Single dose intravenous extended toxicity study in minipigs/ A3733

- Injection site reactions were observed in minipigs given a single intravenous injection of ^{175}Lu-PSMA-617 with PSMA-617 at doses up to 1.8 mg/kg;
- A similar TK profile was observed for ^{175}Lu-PSMA-617 and PSMA-617.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0.2, 0.6, 1.8 mg/kg*, 2.5 mL/kg, single dose [a 1: 1 mixture of ^{175}Lu PSMA-617 and unlabeled PSMA-617] *dose of total PSMA-617 (unlabeled PSMA-617 and ^{175}Lu PSMA-617)
Justification of doses:	Not provided
Route of administration:	intravenous bolus injection
Number/Sex/Group:	5/sex/group
Scheduled terminate	Day 2 (3/sex/group); Day 15 (2/sex/group)
Formulation/Vehicle:	Injection solution/physiological saline (0.9% sodium chloride)
Species/Strain:	minipig
Age:	4-5 months
Deviation from study protocol affecting interpretation of results:	no
Comment on Study Design and Conduct:	none

Table 6. Toxicology observations and results in minipigs/ A3733

Parameters	Major findings
Mortality	none
Clinical Signs	unremarkable
Body weight	unremarkable
Food consumption	unremarkable
Ophthalmoscopy	unremarkable
EKG evaluation	unremarkable
Hematology	unremarkable

Clinical chemistry	unremarkable								
Urinalysis	unremarkable								
Gross Pathology	unremarkable								
Organ Weights	unremarkable								
Histopathology Adequate battery: Yes	Sex	Male				Female			
	Dose (mg/kg)	0	0.2	0.6	1.8	0	0.2	0.6	1.8
	Main (Day 2)								
	Number of animals	3	3	3	3	3	3	3	3
	Injection site								
	Acute inflammation								
	-Minimal or mild		2	2	3	1	2	1	3
	Crust -Minimal	1		1	2	1		1	
	Subcutaneous hemorrhage								
	-Mild or moderate	1	2	3	3	1		1	
	Vascular and perivascular necrosis								
	-Minimal or mild		1	2	3		1	1	2
	Thrombosis -Present				1				1
	Recovery (Day 15)								
	Number of animals	2	2	2	2	2	2	2	2
	Injection site								
	Chronic inflammation								
	-Minimal or mild			2	1	2			
	Crust -Minimal					1	1	1	
	Subcutaneous hemorrhage								
	-Mild or moderate		1		1	2			
	Vascular and perivascular necrosis								
	-Minimal or mild		1	2	1		1		
	Thrombosis -present			1	1				
Toxicokinetics	Refer to ADME/PK section								

Study title/ number: Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats/ 32508

- No toxicity was noted in rats receiving once weekly intravenous administration of PSMA-617 at doses up to 0.4 mg/kg for a total of 4 doses.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0.04, 0.16, 0.4 mg/kg, 5 mL/kg, once weekly, on study days 1, 8, 15 and 22
Justification of doses:	Based on available information on expected human clinical exposure
Route of administration:	Intravenous slow bolus
Number/Sex/Group:	20 males/group
Scheduled terminate	Day 23 (approximately 24 hours after the last administration)
Formulation/Vehicle:	Injection solution/0.9% saline
Species/Strain:	Male rats
Age:	46 days old
Deviation from study protocol affecting interpretation of results:	no
Comment on Study Design and Conduct:	1) Male animals only 2) No TK evaluation

Table 7. Toxicology observations and results in rats/ 32508

Parameters	Major findings
Mortality	none
Clinical Signs	unremarkable
Body weight	unremarkable
Food consumption	unremarkable
Hematology	unremarkable
Clinical chemistry	unremarkable
Urinalysis	unremarkable
Ophthalmological and auditory examination	unremarkable
Gross Pathology	unremarkable
Organ Weights	unremarkable
Histopathology Adequate battery: Yes	unremarkable

The Applicant's Position:

The general toxicity of PSMA-617 and ^{175}Lu-PSMA-617 was assessed in expanded, acute single dose studies in rats and minipigs. Additionally, a repeat dose study of PSMA-617 was conducted in rats. The results of these studies indicated that there is a low risk from exposure to PSMA-617, in its unlabeled or non-radioactive chelated (^{175}Lu-PSMA-617) form, as there were no signs

of systemic toxicologic effects and there were no target organs identified in any study. In the single dose toxicity study in minipigs, the ^{175}Lu-PSMA-617 test solution induced minimal or mild acute inflammation associated with vascular and perivascular necrosis 1 day after administration. Following the 14 days observation period, these reactions were still present at the injection site, but with a recovery trend that was more evident in females than males. The systemic NOAELs identified in toxicity testing equated to significant safety margins relative to a potential maximum human dose of (b) (4) µg when calculated based on body surface area scaling. In the single-dose toxicity studies, safety margins in rats and minipigs were approximately (b) (4) fold and (b) (4)-fold respectively, while the repeat-dose safety margin in rats was (b) (4) fold.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of study results. In the single dose studies in rats and minipigs, the exposure (AUC) multiples of total PSMA-617 (unlabeled PSMA-617 and ^{175}Lu PSMA-617) in rats and minipigs were (b) (4)-fold and (b) (4) fold, respectively, to human exposure of ^{177}Lu-PSMA-617 at the recommended dose.

5.5.2. Genetic Toxicology

Data (presented by FDA):
In vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/number: PSMA-617: Bacterial Reverse Mutation Assay/8365629
Key Study Findings:
• PSMA-617 was not mutagenic under the conditions tested.

GLP compliance: Yes (OECD)
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA102; up to 5000 µg/plate; +/- S9
Study is valid: Yes

The Applicant's Position:
An *in vitro* bacterial reverse mutation assay (Ames test) was conducted with unlabeled PSMA-617, and demonstrated that it was not mutagenic. Additional genotoxicity/mutagenicity studies have not been conducted with ^{177}Lu-PSMA-617 as they are not required according to the relevant guideline: Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations (Guideline for Industry, FDA August 2019). It should be noted that the human drug product ^{177}Lu-PSMA-617 is radioactive, and radiation is considered mutagenic.

The FDA's Assessment:
The FDA agrees with the Applicant's conclusion.

5.5.3. Carcinogenicity

The Applicant's Position:
Carcinogenicity studies have not been conducted with ^{177}Lu-PSMA-617, the unlabeled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617 as they are not required according to the relevant guideline: Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations (Guideline for Industry, FDA August 2019). It should be noted that the human drug product ^{177}Lu-PSMA-617 is radioactive, and radiation is considered carcinogenic.

The FDA's Assessment:
The FDA agrees with the Applicant's conclusion.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:
Reproductive and developmental toxicity studies have not been conducted with ^{177}Lu-PSMA-617, the unlabeled precursor molecule PSMA-617, or non-radioactive ^{175}Lu-PSMA-617 as they are not required according to the relevant guideline: Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations (Guideline for Industry, FDA August 2019).

The FDA's Assessment:
The FDA agrees with the Applicant's conclusion.

5.5.5. Other Toxicology Studies

The Applicant's Position:
No additional toxicology studies have been conducted.

The FDA's Assessment:
The FDA agrees that no additional toxicology studies are warranted.

X X

Wei Chen Tiffany Ricks

Primary Reviewer Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The applicant seeks approval of PLUVICTO (^{177}Lu- vipivotide tetraxetan, also referred to as ^{177}Lu-PSMA-617) for the treatment of patients with prostate specific membrane antigen (PSMA) espressing metastatic castration resistant prostate cancer (mCRPC) and who have previously been treated with androgen receptor pathway inhibition and taxane-based chemotherapy (b) (4) (b) (4) The proposed dosing regimen for ^{177}Lu-PSMA-617 is 7.4 gigabecquerels (GBq) administered as a slow intravenous (IV) push or 30 (b) (4) minute infusion once every 6 weeks for a total of 6 doses (cumulative dose = 44.4 GBq). The proposed dosing regimen is supported by the clinically significant improvement in radiographic progression-free survival (rPFS) and overall survival (OS) and an acceptable safety profile from randomized, active-controlled Study PSMA-617-01 (VISION). This was the only ^{177}Lu-PSMA-617 dosing regimen used in the VISION study.

The primary data to support the Clinical Pharmacology of the drug in the NDA are from the dosimetry/biodistribution, pharmacokinetics (PK), and urine metabolic stability evaluations in the VISION sub-study. The safety data came from the patients enrolled in the VISION study. The selection of the dosing regimen for ^{177}Lu-PSMA-617 was based on available literature data that reported a range of dosing regimens during the planning of VISION study and the phase 2 study that tested 6 and 7.4 GBq given every 8 weeks for 4 cycles. The tolerability of 2 additional cycles with the potential to maximize benefit resulted in the selection of the proposed dosing regimen in the registration trial. No exposure-response analyses for efficacy or safety could be performed due to the limited number of patients (n=30) in the VISION sub-study and no PK sampling was collected in the VISION study.

Exploratory analysis in the VISION sub-study indicated a trend for increased kidney radiation exposure with decreasing creatinine clearance (CLcr). Only one patient with moderate renal function (54 mL/min) enrolled in the vision sub-study had a 2-fold increase in kidney radiation compared to patients with normal renal function (CLcr ≥90 mL/min, n=19). The analysis also showed the potential for cumulative kidney radiation exposure to reach or exceed the radiation safety threshold (23 Gy based on External Beam Radiation Therapy (EBRT)) for the kidney after 5 or 6 doses of ^{177}Lu-PSMA-617 in majority of patients with mild RI and moderate RI. Additionally, in patients with moderate RI (CLcr 59 to 30 mL/min: n=58) administered ^{177}Lu-PSMA-617, higher incidence of myelosuppression, renal toxicity, dose modifications and discontinuations due to adverse reactions (AR) were observed compared to patients with mild RI (n=173) or normal renal function (n=283) in the VISION study. The dosimetry, PK, and safety

of ^{177}Lu-PSMA-617 in patients with severe renal impairment (CLcr 29 to 15 mL/min) have not been studied. Due to the concerns for high kidney radiation exposure, paucity of dosimetry data, and increased toxicity, a post marketing study will be needed to investigate the kidney dosimetry, long-term toxicity, and the potential for dose adjustments or risk mitigation strategies in patients with moderate and severe RI. Frequent monitoring of ARs is recommended for patients with moderate renal impairment receiving ^{177}Lu-PSMA-617.

Exploratory analysis in the VISION sub-study indicated a trend for increased kidney and bone marrow radiation exposure with decreasing body weights. However, no dose adjustment is recommended for patients with lower body weights as there were no clear trends in ARs based on body weight and no increased dose modifications and discontinuations due to ARs based on body weight in the VISION study.

Recommendations

The proposed ^{177}Lu-PSMA-617 dosing regimen of 7.4 GBq as a slow IV push or 30 (b) (4) minute infusion once every 6 weeks for a total of 6 doses is acceptable. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features (b) (4)
☐ PMC ☒ PMR	Evaluation of dosimetry, long-term toxitity, and determination of an appropriate 177Lu-PSMA-617 dose and assessment of risk mitigation strategies in patients with moderate and severe renal impairment.	PSMA is expressed in kidneys and 177Lu-PSMA-617 is mainly excreted renally. Patients with moderate and severe renal impairment appear to have substantially higher cumulative kidney radiation exposure and increased toxicity than patients with normal renal function. Further, radiation exposure often results in long-term kidney toxicity.	

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:
The clinical pharmacology of ^{177}Lu-PSMA-617 has been well characterized. The results from both *in vitro* human biomaterial studies and *in vivo* clinical pharmacology studies were integrated to describe the absorption, distribution, metabolism, and excretion (ADME) properties of ^{177}Lu-PSMA-617 in humans and assess intrinsic and extrinsic factors which may affect the PK of ^{177}Lu-PSMA-617.

In addition, relevant ^{177}Lu-PSMA-617 literature is reviewed as support for the Phase III dose selection, and in conjunction with the internally-derived data, as support for the administration of 7.4 GBq ^{177}Lu-PSMA-617 once every 6 weeks for 6 cycles to PSMA-positive mCRPC patients .

The FDA's Assessment:
Refer to Table A in Section 6.3.1.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:
The recommended dose of ^{177}Lu-PSMA-617 is 7.4 GBq administered once every 6 weeks (± 1 week) for a total of 6 doses.

At the time of the Phase III protocol development, the ^{177}Lu-PSMA-617 dose and administration schedule was based on published clinical studies characterizing the prior safety and efficacy experience with ^{177}Lu-PSMA-617. Further, published radiation dosimetry studies, and a consideration of External Beam Radiation Therapy (EBRT) dose thresholds in organs at risk, provided some general guidance applied to cumulative radiation exposures. Lastly, experience with the approved ^{177}Lu-radioligand therapeutic Lutathera® has provided class-based information.
At present there are a number of publications from retrospective and prospective Phase 1, Phase 2 and dosimetry trials with ^{177}Lu-PSMA-617 which provide a per-cycle dose range (1.1-12 GBq) and a range of time between cycles (4-12 weeks) (Rahbar et al 2017, Demirci et al 2017, Rahbar 2018, Hofman et al 2018, Kim et al 2018, Kulkarni et al 2018b, von Eyben et al 2018, Kessel et al 2019, Grubmüller B et al 2019, Sarnelli 2019, Yadav et al 2019, Violet et al 2020, Yadav et al 2020, Hofman et al 2021, Sadaghiani et al 2021). Also, published clinical studies demonstrated that more than 4 cycles of ^{177}Lu-PSMA-617 could be administered safely as a means to maximize the benefit to the patient (Bräuer et al 2017, Yordanova et al

2017, Kulkarni et al 2018a, Kulkarni et al 2018b, Kulkarni et al 2018c, Rahbar et al 2018, Kessel et al 2019, Van Kalmthout et al 2019, Crumbaker et al 2020, Maffey-Steffan et al 2020, Paganelli et al 2020, Yadav et al 2020, Ahmadzadehfar et al 2021, Hofman et al 2021). In the TheraP (ANZUP1603) study in 200 Australian patients, that compared ^{177}LuPSMA-617 against cabazitaxel, the starting dose was 8.5 GBq ^{177}Lu-PSMA-617 and reduced by 0.5 GBq per cycle, i.e. 8.5, 8, 7.5, 7, 6.5, and 6. Importantly, the final efficacy and safety information from this randomized Phase 2 study demonstrated that this dosing of 6 cycles, for a total cumulative dose of up to 43.5 GBq, was well tolerated and efficacious (Hofman et al 2021). These publications demonstrated signs of efficacy (encouraging biochemical and radiographic response rates, overall survival and reduced pain), while maintaining safety parameters which are appropriate for the mCRPC patient population.

^{177}Lu-PSMA-617 dosimetry study results reported in the literature have identified the salivary glands, lacrimal glands, kidneys and bone marrow as the organs considered at risk from radiation due to their exposure levels as compared to non-RLT historical radiation thresholds. At the time of protocol development, the direct application of these thresholds to ^{177}Lu-PSMA-617 treatment regimens, as well as those used with other RLT agents like Lutathera, was considered to be overly conservative due to the significant differences in radiation exposure (eg., dose rate) of these therapies relative to EBRT. Further, in an mCRPC patient population at extremely high risk from their disease, such dosing limitations may not be appropriate, where efficacy in the near term is critical to extending a patient's overall survival. By applying the mean dosimetry estimates from the PSMA-617-01 sub-study, the mean cumulative exposure to these tissues from 6 cycles of 7.4 GBq was either below, or only marginally higher than the non-RLT cumulative radiation thresholds. Of note is that lacrimal glands, although estimated to potentially exceed the EBRT threshold after 6 cycles of treatment, have not routinely been utilized to limit ^{177}Lu-PSMA-617 dosing regimens, perhaps due to some of the challenges around accurate radioactivity quantification to this tissue, as well as a lack of reported AEs.

Additionally, clinical safety data for the approved ^{177}Lu-radioligand therapeutic, Lutathera showed that no patients in the NETTER-1 study developed Grade 3/4 renal toxicity, or had a marked reduction in CLcr based on assessments every 6 months in the 5 year follow-up period of the study. This was after following a dose of 7.4 GBq every 8 weeks, for a total of 4 cycles (29.6 GBq cumulative activity, for a calculated cumulative absorbed dose of 19.4 ± 8.7 Gy in the kidneys). A similar profile was expected with ^{177}Lu-PSMA-617, as both the compounds are ^{177}Lu-radioligand therapeutics, with the same route of excretion, and with similar renal absorbed dose levels.

As stated above, the dosimetry data from 29 patients in the PSMA-617-01 sub-study are available which support the use of the selected dose of 7.4 GBq every 6 weeks (± 1 week) for a total of 6 doses from a radiation exposure perspective. This is in addition to the PSMA-617-01

main-study confirming efficacy and tolerability and a positive risk-benefit with the selected 7.4 GBq dose and regimen of 6 total doses.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding the proposed ^{177}Lu-PSMA-617 dose of 7.4 GBq administered once every 6 weeks for a total of 6 doses, based on the demonstration of favorable efficacy and safety in the VISION Study.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:
No therapeutic individualization is needed in the proposed indication based on demographic factors, DDIs that may affect ^{177}LuPSMA-617 pharmacokinetics (or biodistribution), or in special populations.

The FDA's Assessment:
FDA agrees with the Applicant's position of no dose modifications based on age (32 to 90 years), body weight (41 to 158 kg), and mild (creatinine clearance (CLcr) 60 to 89 mL/min) and moderate renal impairment (CLcr 30 to 59 mL/min) (refer to Section **Error! Reference source not found.** for details). Frequent monitoring of adverse reactions (AR) is recommended for patients with moderate renal impairment receiving ^{177}Lu-PSMA-617. The dosimetry, PK, and safety of ^{177}Lu-PSMA-617 in patients with severe renal impairment (CLcr 29 to 15 mL/min) have not been studied.

Limited dosimetry data in the VISION substudy and safety data in the VISION study indicated potential for increased radiation exposure to the kidneys, and increased incidence of toxicity and dose modifications and dose discontinuations due to toxicity in patients with moderate renal impairment (refer to Section **Error! Reference source not found.** for details). However, no dose adjustment is recommended in patients with moderate renal impairment as only one dose was tested in the VISION study, and limited efficacy data is available for less than six doses and for dose reductions in the VISION trial. Therefore, due to the potential for long-term toxicity with high radiation exposure, additional information regarding kidney dosimetry, long-term safety of ^{177}Lu-PSMA-617, and potential for dose adjustment of ^{177}Lu-PSMA-617 and risk mitigation strategies in patients with moderate and severe (CLcr 29 to 15 mL/min) renal impairment will be needed as a post-marketing requirement (refer to Section **Error! Reference source not found.**.2.3 for details).

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The FDA agrees with the Applicant's position that no dose modifications are necessary with the concomitant use of CYP modulators and the concomitant use of drugs that are substrates of

CYP enzymes and transporters.

6.2.2.3. Outstanding Issues

The Applicant's Position:
None.

The FDA's Assessment:
FDA disagrees with the Applicant's position in that there is insufficient data to assess the radiation exposure to the kidneys and long term safety, and the potential for dose adjustment of ^{177}Lu-PSMA-617 and risk mitigation strategies in patients with moderate and severe renal impairment for the following reasons (refer to Section **Error! Reference source not found.** for details):

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- Only one patient with moderate renal impairment (CLcr 54 mL/min) was enrolled in the VISION sub-study. Dosimetry results demonstrated ~2-fold increase in kidney radiation exposure in this patient compared to patients with normal renal function.
- Cumulative radiation exposure was observed to reach or exceed the safety radiation threshold in majority of patients with mild renal impairment and in the patient with moderate renal impairment after the 5th and 6th ^{177}Lu-PSMA-617 doses.
- Increased toxicity, and dose modification and discontinuations due to toxicities were observed in patients with moderate renal impairment in the VISION study.
- Patients with severe renal impairment were not enrolled in the VISION study or the sub-study.
- Patients with severe renal impairment are prevalent in the proposed disease population, and could potentially benefit from ^{177}Lu-PSMA-617 therapy.

Therefore, a post-marketing study will needed to assess these issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
An overview of the ADME properties, clinical pharmacokinetics, and DDI potential of 177Lu-PSMA-617 is provided below.

Absorption: ^{177}Lu-PSMA-617 is administered intravenously, the bioavailability is 100% and no food effect would be anticipated. Hence, no biopharmaceutic studies have been carried out with ^{177}Lu-PSMA-617.

Distribution:
The geometric mean (CV%) volume of distribution (Vz) was 123 L (78.1%) based on the PSMA-617-01 sub-study results. Unlabeled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617 were moderately bound to human plasma proteins following incubation for 30 minutes at 37°C. The bound fraction observed in human plasma for both PSMA-617 and ^{175}Lu-PSMA-617 was 70% and ~60% at 1 and 5 µg/mL, respectively. Additionally, the blood/plasma partitioning ratio of both PSMA-617 and ^{175}Lu-PSMA-617 in human blood was <1, indicating that ^{175}Lu-PSMA-617 was not distributed to human erythrocytes.
The distribution of ^{177}Lu-PSMA-617 to normal tissues was evaluated in a 29 patient sub-study. On average, the organs receiving the largest absorbed doses were the lacrimal glands at 2.1 (SD=0.47) Gy/GBq followed by the salivary glands at 0.63 (SD=0.36) Gy/GBq. For a full six cycle cumulative administration of 44.4 GBq, the calculated estimated absorbed dose for lacrimal glands and salivary glands were 92 (SD=21) Gy and 28 (SD=16) Gy, respectively. Red marrow received an absorbed dose of 0.035 (SD=0.020) Gy/GBq, with a full six cycle calculated estimated absorbed dose of 1.5 (SD=0.90) Gy. On average, the kidneys received 0.43 (SD=0.16) Gy/GBq, which for a full six cycle cumulative administration of 44.4 GBq, results in a calculated estimated absorbed dose to the kidneys of 19 (SD=7.3) Gy.

Metabolism:
Results from in vitro metabolism studies showed that both unlabeled PSMA-617 and non-radioactive ^{175}Lu-PSMA-617 were metabolically stable in human liver and kidney S9 fractions for up to 1 hour at 37°C and in human plasma at 37°C for up to 2 hours. ^{177}Lu-PSMA-617 demonstrated metabolic stability in vivo, as analyses of blood and urine samples showed a single radioactivity peak even at 24 hours after injection/infusion (Kabasakal et al 2017), in line with findings from the PSMA-617-01 sub-study metabolite analysis in urine showing no major excretion of metabolites up to 48 hrs.
As only a very minor fraction of radioactivity is eliminated in feces, according to literature, it can be concluded that 177Lu-PSMA-617 is not metabolized in vivo in systemic circulation, in the liver or in the kidneys.

Excretion:
The excretion of ^{177}Lu-PSMA-617 occurs primarily through kidneys, and it is eliminated in the urine mainly as an unchanged molecule, as shown in the urinary metabolite analysis from the PSMA-617-01 sub-study, as well as the literature (Kabasakal et al 2017). Approximately half of the injected amount of ^{177}Lu-PSMA-617 was excreted within 24-48 hours (Kratochwil et al 2016, Kabasakal et al 2017), in line with derived geometric mean terminal elimination half-life of 41.6 hrs. According to Kratochwil et al (2016) only an estimated 1%–5% of the injected dose was eliminated by fecal excretion.

Clinical pharmacokinetics:
Following an IV injection/infusion of ^{177}Lu-PSMA-617, time to peak whole blood concentrations (T_{max}) ranged from 0.0167 to 1.68 hours, generally occurring within approximately 20 minutes

after the end of infusion, with median T_{max} value of 0.375 hours. Whole blood concentrations followed a bi-exponential decline with a fast phase within the first 24-48 hrs and a slower phase up to 144 hrs, which resulted in a geometric mean (geometric mean CV%) terminal elimination half-life of approximately 41.6 hr (68.8%) hours. The effective half-live accounting for the decay of Lu-177 radioactivity was ~33 hours. The geometric mean total systemic clearance (CL) was 2.04 L/hr (31.5%) and geometric mean apparent volume of distribution (Vz) was 123 L (78.1%).

The FDA's Assessment:
Refer to information in Table A below.

Table 8: Summary of General Pharmacology and Pharmacokinetic Characteristics of ^{177}Lu-vipivotide tetraxetan (*a.k.a.* ^{177}Lu-PSMA-617)

Note: PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted

Pharmacology	
Mechanism of Action	^{177}Lu-PSMA-617 binds to PSMA (Ki ~4.7 nM) in PSMA-expressing prostate cancer cells. Uptake of ^{177}Lu-PSMA-617 into PSMA expressing tumor cells was ~55–70%, while the internalized fraction was about 10% to 15% of total added radioactivity in vitro.
Active Moieties	^{175}Lu-PSMA-617 and unlabeled PSMA-617 at 1 µM (~1 µg/mL) were found to be stable in human plasma for 2 hours at 37°C and metabolically stable in human liver and kidney S9 fractions.
QT Prolongation	^{177}Lu- vipivotide tetraxetan does not cause large mean increases (>20 ms) in the QTc interval.
General Information	
Bioanalysis	Whole blood concentrations of ^{177}Lu- vipivotide tetraxetan in VISION substudy were determined by measuring total radioactivity, expressed as KBq/mL, using a gamma counter, and converted to ng/mL using specific activity and decay corrected radioactivity. ^{177}Lu- vipivotide tetraxetan in human urine in VISION substudy was determined using a validated high performance liquid chromatography with in-line radiodetection of parent drug and metabolites.
Healthy vs. Patients	No healthy volunteer studies were conducted with ^{177}Lu- vipivotide tetraxetan
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Multi-dose PK samples were not collected given that ^{177}Lu- vipivotide tetraxetan was administered every 6 weeks. Based on single dose PK, the mean (%CV) AUC_{0-inf} of ^{177}Lu- vipivotide tetraxetan at the recommended is 52.3 ng.h/mL (31.4%) and mean C_{max} is 6.58 ng/mL (43.5%)
Dose Proportionality	Only one dose was tested in the VISION sub-study.
Accumulation	Only single dose was tested in the VISION sub-study. Base on the terminal half-life and dosing interval of 6 weeks, no accumulation in AUC is expected.
Variability	^{177}Lu- vipivotide tetraxetan CV was 31% for AUC_{0-inf} and 44% for C_{max}..
Absorption	

Adminsitration	^{177}Lu- vipivotide tetraxetan was administered as a slow IV push or 30(b) (4) minute IV infusion
Median T_{max}	0.375 hours (range: 0.0167 – 1.68 hours)
Distribution	
Volume of Distribution	123 L (78.1%)
Plasma Protein Binding	70% and ~60% at 1 and 5 µg/mL for PSMA-617 and ^{175}Lu-PSMA-617, respectively
Human Blood to Plasma Ratio	0.28 (25%) for PSMA-617 and 0.49 (2%) for ^{175}Lu-PSMA-617
As Substrate of Transporters	Vipivotide tetraxetan is not a substrate of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3 or OCT2
Elimination	
Terminal Elimination Half-Life	41.6 (68.8%) hours.
Metabolism	
Fraction Metabolized (% dose)	Parent drug was the primary component in urine. Literature data indicates that ~50% of the injected activity was eliminated by urine during the first 48 hours, with 1-5% injected dose excreted in feces▲,*. Urine collections were not cumulative, except for 0-2 hour collection, in VISION substudy.
Primary Metabolic Pathway(s)	^{175}Lu-PSMA-617 and unlabeled PSMA-617 at 1 µM (~1 µg/mL) were found to be metabolically stable in human liver and kidney S9 fractions. Parent drug expressed as percent of total radioactivity in each sample were 96 ± 1.6 % in 0-2 hour sample, 93 ± 3.5 % at 24 hour sample, 84 ± 7.9 % at 48 hour sample, and 68 ± 14.3 % at 72 hour sample. M1, M3, and M4 were the primary metabolitic or chemical hydrolysis products at 72 hour post-dose. Literature indicates that urine samples showed a single ^{177}Lu-PSMA-617 radioactive peak at 24 hours post injection▲.
Excretion	
Primary Excretion Pathways (% dose) ±SD	Primary route of elimination of ^{177}Lu- vipivotide tetraxetan is renal. 96 ± 1.6 % (range 91% - 100%) of total radioactivity was unchanged ^{177}Lu-vipivotide tetraxetan in the 0-2 hour urine sample.
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	Vipivotide tetraxetan did not induce CYP1A2, 2B6 or 3A4; and did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A *in vitro*
Inhibition/Induction of Transporter Systems	Vipivotide tetraxetan is not an inhibitor of BCRP, P-gp, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 or OCT2 *in vitro*

†Kractochwil *et al*. (2016). *J. Nucl. Med.* 57 (8):1170-76.
▲Kabaskal et a. (2017). *Mol Imaging Radionucl. Ther.* 26:62-68
$AUC_{0\text{-}inf}$ = area under concentration curve from time 0 to infinityval; C_{max}=maximum plasma concentration

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The results from Study PSMA-617-01 provide evidence of positive benefit-risk supporting 7.4 GBq ^{177}Lu-PSMA-617 every 6 weeks for a total of 6 doses in adult patients with PSMA-positive mCRPC. A clinical pharmacology evaluation of exposure-efficacy has not been conducted, however efficacy results from Study PSMA-617-01 support the proposed dose and regimen (7.4 GBq (200 mCi) every 6 weeks (± 1 week) for a total of 6 cycles of ^{177}Lu-PSMA-617), and additional evidence for using a total of 6 cycles in patients is also provided by the following sub-group analyses from Study PSMA-617-01, in the 69 patients who received 4 cycles, and the 289 patients who received 5-6 cycles (FAS Safety set) (Section 8.1.2: Additional Analyses Conducted on the Individual Trial).

The FDA's Assessment:

FDA agrees with the Applicant's position that the acceptability of the dose for ^{177}Lu-vipivotide tetraxetan was based on the results of primary endpoints (rPFS and OS) favouring the treatment arm compared to the control arm in the VISION study (refer to Section 8.1) and no exposure-response analysis for either efficacy or safety could be performed as PK samples were collected in only a limited number of patients (6%: n=30) in the VISION sub-study.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed dose of 7.4 GBq ^{177}Lu-PSMA-617 administered once every 6 weeks (Q6W) for 6 cycles is effective and well-tolerated in PSMA-positive mCRPC patients. Alternative dosing regimens were not explored as part of the Phase III study, however in the literature a range of dose levels, cycle number, and time between doses have been reported to be safe and efficacious in a similar population. The safety signals which were identified in PSMA-617-01 were consistent with the general distribution of ^{177}Lu-PSMA-617 and its mechanism of action. Details of AEs are provided in Section 8.2.4.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations.

Demographic Factors

Population PK and dosimetry analyses showed that ^{177}Lu-PSMA-617 exposure and biodistribution are not affected by body weight or body mass index. Since ^{177}Lu-PSMA-617 is not metabolized by the liver and is eliminated passively through renal excretion, PK is unlikely to be affected by ethnic factors. Age, in the range of 52 to 80 years (median 67 years) in the PSMA-617-01 sub-study, was not found as a statistically significant covariate in the ^{177}Lu-PSMA-617 population PK model. Use of ^{177}Lu-PSMA-617 in the pediatric population is not relevant and hence was not studied.

Special Population

- **Impaired renal function:** No dedicated renal impairment study for ^{177}Lu-PSMA-617 has been conducted. Simulations were performed to explore the effect of renal impairment on ^{177}Lu-PSMA-617 PK exposure. Among the 30 sub-study patients, one (3.3%) and 10 (33.3%) patients had moderate and mild renal impairment, respectively, while 19 (63.3%) patients had normal kidney function. Mild to moderate renal impairment seems to affect kidney absorbed dose. However, the clinical relevance of this finding is difficult to interpret as there is no clear relationship established between kidney dosimetry and clinical safety. Based on observed value of kidney absorbed dose and the distribution observed for mild impairment (population PK analysis) in a moderate renal impaired patient, and since no clinically significant renal toxicity was observed in Study PSMA-617-01, it can be concluded that mild and moderate renal impairment are unlikely to warrant any dose adjustments. No information is available for severe renal impairment or end-stage renal disease.

- **Impaired hepatic function:**

  Preclinical and clinical experience with ^{177}Lu-PSMA-617 showed that liver metabolism of the compound is negligible, and the liver is not the primary organ responsible for clearance and excretion (Kratochwil et al 2016). Hence, hepatic impairment is unlikely to significantly alter the PK of ^{177}Lu-PSMA-617. In accordance with hepatic impairment guidances (i.e. hepatic metabolism and/or excretion <20% of the absorbed drug, no narrow therapeutic index) a dedicated study in patients with liver impairment is not considered necessary and thus not conducted (FDA 2003, EMA 2005).

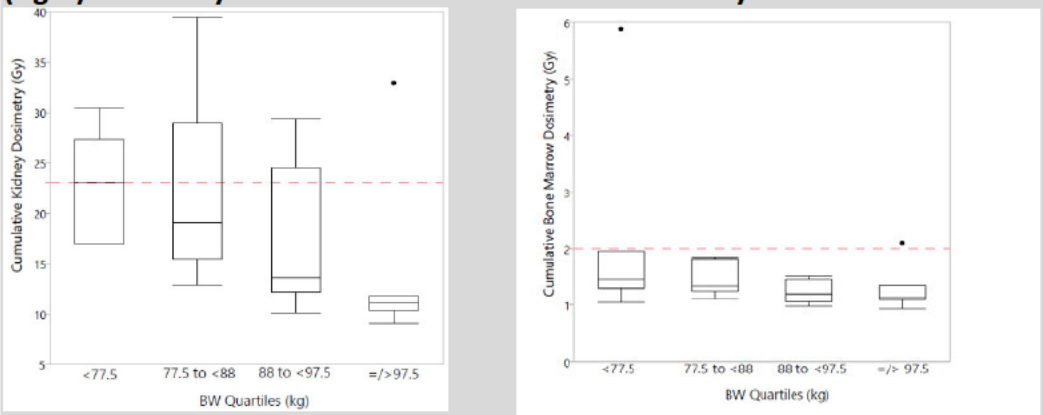
  No dose adjustment is therefore needed for any degree of hepatic impairment.

The FDA's Assessment:

FDA agrees with the Applicant's position in that no dose adjustment is necessary for patients with low body weights, hepatic impairment, and mild to moderate renal impairment. However, FDA disagrees with the Applicant's position in that there was increased incidence of ARs and dose modifications and discontinuations due to ARs in patients with moderate renal impairment compared to patients with normal renal function in the VISION study. Additionally, the limited dosimetry data showed a trend for increased kidney radiation absorbed dose with renal impairment, with a ~2-fold increase in kidney radiation exposure in the one patient enrolled with moderate renal impairment compared to patients with normal renal function in the VISION sub-study. No dose adjustment is recommended in patients with moderate renal impairment as only one dose was tested in the VISION study, and limited efficacy data is available for less than six doses and for dose reductions in the VISION trial. Nonethless, frequent monitoring of adverse events is recommneded for patients with moderate renal impairment. The dosimetry, PK, and safety of ^{177}Lu-PSMA-617 has not been studied in patients with severe renal impairment.

Due to the potential for increased radiation exposure to the kidneys with renal impairment and long-term toxicity, and paucity of dosimetry data in patients with moderate and severe renal impairment, post marketing studies will be needed to evaluate the dosimetry and potential for long-term toxicity due to radiation exposure and the need for dose adjustment of ^{177}Lu-PSMA-617 and/or risk mitigation strategies in patients with moderate and severe renal impairment who receive ^{177}Lu-PSMA-617.

Figure 1: Relationship between body weight and cumulative kidney (left) and bone marrow (right) dosimetry after six doses in the VISION sub-study



Dashed red line represents the external beam radiation threshold (EBRT) for kidneys and threshold based on iodine therapy for bone marrow. BW = body weight
Source: Reviewer's analysis

Table 9: Summary of safety of patients who received 177Lu-PSMA-617 by body weight in

VISION study.

AR (% Patients)	Lu-PSMA-617+SoC				SoC only			
	<75.4 kg (n=131)	≥75.4 <85.6 kg (n=124)	≥85.6 <97.1 kg (n=131)	≥97.1 kg (n=128)	<75.4 kg (n=47)	≥75.4 <85.6 kg (n=54)	≥85.6 <97.1 kg (n=47)	≥97.1 kg (n=50)
Total	97	98	98	100	85	82	85	80
Grade ≥3 AR	56	50	50	52	40	43	38	34
Serious AR	37	41	36	31	34	33	19	28
AR→ Discontinuation	16	8	15	8	0	0	0	2
AR→ Dose Interruption	18	12	18	15	2	0	0	2
AR→ Dose Reduction	8	11	3	2	0	0	0	0
AE→ Discont.	12	7	8	8	9	9	6	8
AE→ Dose Interrup.	10	7	12	9	9	7	6	4
AE→ Dose Reduc.	4	2	2	6	4	2	2	4

AR refers to adverse reactions; → denotes 'leading to'
Source: Table 2.2, SDN 20

Effect of Body weight:
Exploratory analysis indicates a trend for higher radiation exposure to kidney and bone marrow with decrease in body weight, with cumulative radiation exposure reaching or exceeding the radiation threshold in the lower body weight quartiles (Figures A). The inference of lack of effect of body weight on PK of lutetium (^{177}Lu) vipivotide tetraxetan based on population PK analysis should be interpreted with caution due to the limited data set. However, comparison of safety between body weight quartiles of patients who received ^{177}Lu-PSMA-617 in the VISION study did not indicate a trend for higher Grade ≥3 and serious ARs, and discontinuations and dose interruptions due to ARs in the lower body weight quartiles. Although, the incidence of dose reductions due to ARs was higher in the lower body weight quartiles, the overall incidence was low (~10%) (Table B).

Table 10: Summary of safety of patients who received 177Lu-PSMA-617 by age in VISION study

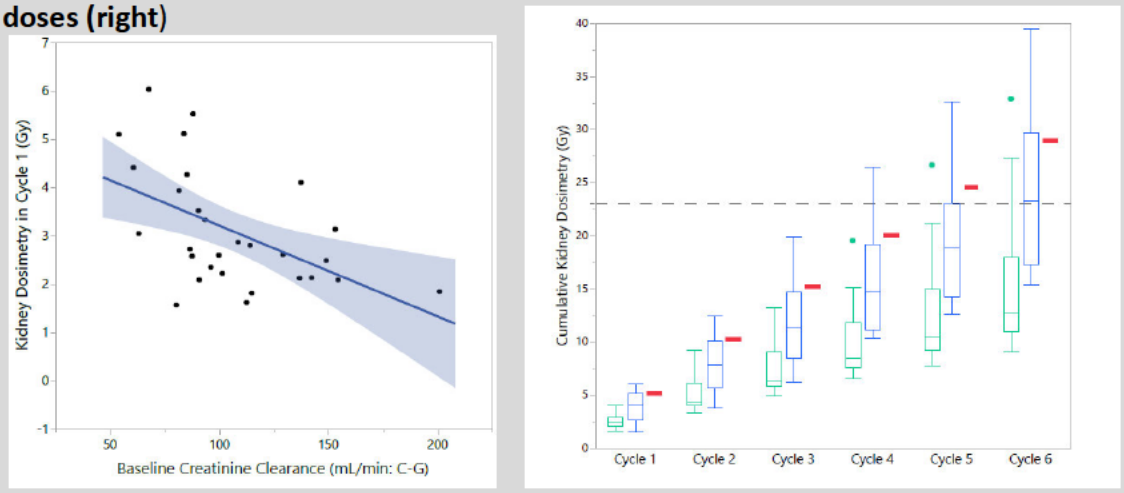
AE (% Patients)	Lu-PSMA-617+SoC				SoC only			
	≤64 yrs (n=142) %	>64 to ≤70 yrs (n=138) %	>70 to ≤75 yrs (n=137) %	>75 yrs (n=112) %	≤64 yrs (n=42) %	>64 to ≤70 yrs (n=54) %	>70 to ≤75 yrs (n=54) %	>75 yrs (n=55) %
Total	97	99	99	100	81	81	94	93
Grade ≥3 ARs	52	52	61	54	43	37	35	49
Serious ARs	32	36	46	38	24	26	30	42
AR→ Discontinuation	10	14	10	14	0	0	1	0
AR→ Dose Interruption	15	19	15	17	0	0	1	1
AR→ Dose Reduction	5	2	9	7	0	0	0	0

AR refers to adverse reactions; → denotes 'leading to'
Source: Reviewer's analysis

Effect of Age

The inference of the effect of age on the PK of lutetium (^{177}Lu) vipivotide tetraxetan based on population PK analysis should be interpreted with caution due to the limited data set. Nonetheless, summary safety analysis of patients who received ^{177}Lu-PSMA-617 in the VISION trial did not show any trends in the incidence of ARs and dose modification and discontinuations due to ARs with age (Table C).

Figure 2: Relationship between baseline creatinine clearance and kidney radiation exposure after first dose (left) and renal impairment and cumulative kidney radiation exposure after six doses (right)



Dased line represents the external beam radiation threshold (EBRT) for kidneys; RI refers to renal impairment
Source: Reviewer's analysis

Table 11: Summary of safety of patients who received 177Lu-PSMA-617 by renal impairment in the VISION Study

AR (% Patients)	Lu-PSMA-617+SoC			SoC only		
	Normal (n=283)	Mild (n=173)	Moderate (n=58)	Normal (n=101)	Mild (n=68)	Moderate (n=29)
Total	98	99	97	75	90	93
Grade ≥3 AR	49	54	**60**	33	43	52
Serious AR	32	39	**47**	21	35	41
AR→ Discontinuation	10	10	**24**	-	-	-
AR→ Dose Interruption	12	17	**28**	-	-	-
AR→ Dose Reduction	3	8	**12**	-	-	-
Anemia	27	35	**47**	12	12	24
Thrombocytopenia	15	18	**26**	5	4	4
Neutropenia	8	8	**14**	2	2	0
≥ 1 Renal effects	4	11	**22**	0	4	31

↑Blood Creatinine	3	7	**12**	0	0	17
Acute Kidney Inj.	1	4	**12**	0	4	17

AR refers to adverse reactions; → denotes 'leading to'; RI refers to renal impairment
Source: 8.1.3a & 8.1.3.b, SDN 18: Table 2-2, SDN 29

Effect of Renal Impairment:

The VISION substudy included 19 patients with normal renal function (CLcr ≥ 90 mL/min), 10 patients with mild renal impairment (CLcr: 60-89 mL/min), and only one patient with moderate renal impairment (CLcr 54 mL/min). Exploratory analysis indicated that kidney dosimetry was higher in patients with decreasing CLcr, with about a two-fold increase in cumulative kidney radiation exposure in the patient with borderline moderate renal impairment compared to patients with normal renal function, irrespective of the number of ^{177}Lu-PSMA-617 doses received (Figure C). Further, radiation exposure was observed to reach or exceed the radiation threshold in majority of patients with mild and moderate renal impairment after the 5th and 6th ^{177}Lu-PSMA-617 doses. A comparative analysis of safety in patients who received ^{177}Lu-PSMA-617 in VISION study based on renal function categories revealed a consistently higher incidence of Grade ≥3 and serious ARs, myelosuppression, renal toxicity, and discontinuations and dose modifications due to ARs in patients with moderate renal impairment (n=58) compared to patients with normal renal function (n=283) and mild renal impairment (n=173) (Table D). No patients with severe renal impairment were enrolled in the VISION study.

Although majority of the patients with moderate renal impairment had lower body weights, lower body weight alone may not explain the increase in ARs and dose modification and discontinuations observed in these patients (Table E).

Table 12: Summary of safety of patients with moderate renal impairment who received 177Lu-PSMA-617 by body weight in the VISION Study

	Lu-PSMA-617+SoC			
AE (% Patients)	**Overall** (n=529)	**Moderate RI** (n=58)	**Moderate RI BW<85.6** (n=49)	**Moderate RI BW≥85.6** (n=9)
Total	97	97	98	100
Grade ≥3 ARs	53	60	63	15
Serious ARs	36	47	47	56
AR→ Discontinuation	12	24	16	67
AR→ Dosage Interruption	16	28	26	33
AR→ Dose Reduction	6	12	14	0

AR refers to adverse reactions; → denotes 'leading to'; RI refers to renal impairment
Source: Reviewer's Analysis

Therefore, post marketing studies will be needed to evaluate the dosimetry and potential for

long-term toxicity due to radiation exposure and the need for dose adjustment of ^{177}Lu-PSMA-617 and/or risk mitigation strategies (e.g., exogenous amino acids, PSMA inhibitors, or unlabeled PSMA-617) in patients with moderate and severe renal impairment who receive ^{177}Lu-PSMA-617.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Food Effect

As ^{177}Lu-PSMA-617 is administered intravenously, no food effect is expected.

Co-administration with other medications

As ^{177}Lu-PSMA-617 is metabolically stable both *in vitro* and *in vivo*, passively cleared via the kidney and not a substrate of any of the investigated uptake or efflux transporters based on in vitro assessments using a non-radioactive formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, it is unlikely to become subject to any metabolic- or transporter-mediated drug interactions in vivo.

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

Effect of ^{177}Lu-PSMA-617 on concomitant medications/Effect of ^{177}Lu-PSMA-617 on CYP3A4 substrates

Based on the risk assessment of *in vitro* data using a non-radioactive formulation containing unlabeled PSMA-617 and ^{175}Lu-PSMA-617, ^{177}Lu-PSMA-617 is not an inducer of CYP1A2, 2B6 and 3A4 and was also not an inhibitor of all common CYPs and investigated efflux and uptake transporters at ^{177}Lu-PSMA-617 and total peptide concentrations achieved with a clinical 7.4

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

The FDA's Assessment:
FDA agrees with the Applicant's position in that in vitro studies indicate that vipivotide tetraxetan is not likely a substrate or perpetrator of major CYP enzymes and transporters. FDA cannot confirm the Applicant's position regarding the lack of effect of androgen receptor pathway inhibitors on dosimetry and PK of ^{177}Lu-PSMA-617 due to the limited data in the VISION sub study.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:
All studies pertinent to the evaluation of efficacy and safety are summarized in Table 13.

Table 13: Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
Pivotal study – VISION (PSMA-617-01) Ongoing, recruitment complete; Final analysis complete; DCO 27-Jan-2021	NCT03511664	Phase III, multi-center, open-label, randomized study to evaluate the efficacy, safety and tolerability of ^{177}Lu-PSMA-617 / Male adult patients with progressive PSMA-positive mCRPC previously treated with 1 to 2 taxane regimens and	Arm 1: ^{177}Lu-PSMA-617+BSC/BSoC: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 iv every 6 weeks (±1 week) for a maximum of 6 cycles + BSC/BSoC as per physician's discretion and protocol at the institution Arm 2: BSC/BSoC Only:	*Primary*: rPFS and OS (alternate primary endpoints). *Key secondary*: ORR (CR+PR), DCR (CR+PR+SD) as measured by RECIST v1.1 and time to a first SSE *Other Secondary*: Safety, tolerability, HRQoL, PFS, PSA response.	14 months to randomize patients in the study. After the last patient is randomized, patients were to be followed for up to 24 months or at least until 508 deaths had occurred. The maximum duration of the study, from first date of randomization to last follow-up, will therefore be	Randomized: N=831 (N=551 investigational arm; N=280 control arm) FAS Safety Analysis Set (treated): N=734 (N=529 investigational arm; N=205 control arm)	Adult male with progressive PSMA-positive mCRPC who received at least one NAAD and 1 to 2 taxane-based chemotherapy regimens	Belgium (3); Canada (7); Denmark (3); France (6); Netherlands (4); Sweden (5); UK (9); US (45)

		at least one novel androgen axis drug (NAAD)	BSC/BSoC as per physician's discretion and protocol at the institution		approximately 38 months			
		Studies to Support Safety						
RESIST-PC (PSMA-617-02) Terminated early: 22-Jun-2018 Final analysis complete; DCO 15-Jan-2020	NCT03042312	Phase II, bi-centric, open-label, nonrandomized study to evaluate the safety and efficacy of ^{177}Lu-PSMA-617 / Patients with progressive PSMA-positive mCRPC previously treated with ≥1 NAAD and either taxane-naive or taxane-treated	Arm 1: 6.0 GBq (±10%) ^{177}Lu-PSMA-617 iv every 8 weeks (±1 week) until reaching 4 cycles or threshold maximum dose to the kidneys of 23 Gy Arm 2: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 iv every 8 weeks (±1 week) until reaching 4 cycles or threshold maximum dose to the kidneys of 23 Gy	*Primary Objectives*: 12 week PSA response Clinical safety *Secondary Objectives*: Maximum PSA response, PSA PFS, rPFS, DCR, QoL, pain scores, ECOG. Since the study was terminated early, the study results will be provided as an abbreviated study report, focusing on safety results.	Study was terminated early (enrollment ended as of 22 Jun 2018).	Randomized: N=71 Treated: N=23 (Arm 1) N=41 (Arm 2)	Adult males with progressive PSMA-positive mCRPC after at least one NAAD and either chemotherapy naïve or post-chemotherapy	United States (California, Texas)

		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
VISION PSMA-617-01 Sub-study Ongoing, recruitment complete; Primary analysis complete; DCO 27-Jan-2021	NCT03511664	A dosimetry, PK and ECG sub-study conducted in a non-randomized cohort of approximately 30 patients treated with ^{177}Lu-PSMA-617+BSC/BSoC at sites in Germany / Male adult patients with progressive PSMA-positive mCRPC previously treated with 1 to 2 taxane regimens and at least one novel androgen axis drug (NAAD)	Arm 1: ^{177}Lu-PSMA-617+BSC/BSoC: 7.4 GBq (±10%) ^{177}Lu-PSMA-617 iv every 6 weeks (±1 week) for a maximum of 6 cycles + BSC/BSoC as per physician's discretion and protocol at the institution	*Primary*: Whole body and organ radiation dosimetry of ^{177}Lu-PSMA-617 up to C1D8. *Secondary*: Pharmacokinetics, ECG, safety, tolerability, and metabolic stability of ^{177}Lu-PSMA-617 up to C1D8.	Same as PSMA-617-01	N=30, non-randomized to Investigational arm[1]	Adult male with progressive PSMA-positive mCRPC who received at least one NAAD and 1 to 2 taxane-based chemotherapy regimens	Germany

1- Dosimetry was performed in 29 patients and PK in 30 patients

The Applicant's Position:

Only data from the pivotal study Phase III Study PSMA-617-01 is included in this document. Exposure to study treatment in Study PSMA-617-01 was considered appropriate to allow for an adequate assessment of safety in subjects who were representative of the intended target population. Hence, data from the Study PSMA-617-01 is being discussed here. To note, in the PSMA-617-02 study, the demographic characteristics were representative of the mCRPC population, and were generally balanced between the 2 treatment arms. The study was terminated early and consequently, the number of patients were low; hence, it was not possible to draw any meaningful comparison. This study did not contribute towards efficacy analysis as it did not provide any additional efficacy data to support treatment with ^{177}Lu-PSMA-617+Best Supportive(BSC)/Best Standard of Care (BSoC). The safety profile of ^{177}Lu-PSMA-617 in PSMA-617-02 was as anticipated based on the mechanism of action and is generally consistent with and in support of the PSMA-617-01 study results.

The FDA's Assessment: The Phase III VISION trial provides the primary evidence basis to evaluate the safety and efficacy of the investigational agent for this NDA. Note that the Applicant submitted the dosimetry data from VISION Sub-study on October 27th after the midcycle meeting (See the Clinical Pharmacology section).

8 Statistical and Clinical Evaluation

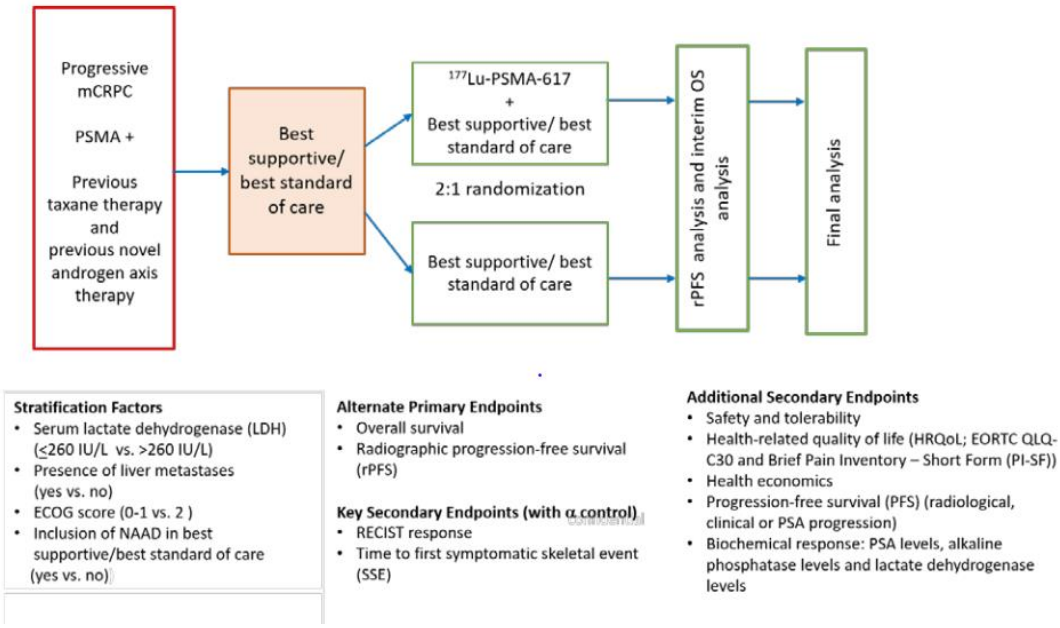
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PSMA-617-01

Trial Design

This was a Phase III, open-label, international, randomized study to evaluate the efficacy and safety of ^{177}Lu-PSMA-617 in patients with progressive PSMA-positive mCRPC, when administered in addition to BSC/BSoC as compared to BSC/BSoC only Figure 3.

Figure 3: Study design



ECOG = Eastern Cooperative Oncology group; EQ-5D-5L = European Quality of Life (EuroQol) – 5 Domain 5 Level scale; FACT-P = Functional Assessment of Cancer Therapy – Prostate; mCRPC = metastatic castrationresistant prostate cancer; PSMA+ = prostate-specific membrane antigen positive; RECIST = Response Evaluation Criteria in Solid Tumors

Screening and randomization

At screening, potential patients were assessed for eligibility and had to undergo a ^{68}Ga-PSMA-11 PET/CT scan to evaluate PSMA positivity per the pre-defined read rules, by the Sponsor's central reader. Only patients with PSMA-positive metastatic PC and meeting all other

inclusion/exclusion criteria were randomized in a 2:1 ratio to receive either ^{177}Lu-PSMA-617 plus BSC/BSoC or BSC/BSoC only. Randomization was stratified by the following 4 factors:

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

BSC/BSoC included available care for the eligible patient according to best institutional practice and at the discretion of the investigator. NAADs (i.e., enzalutamide or abiraterone) were allowed. Investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. radium-223) or hemi-body radiotherapy treatment were not administered during the study.

BSC/BSoC for each patient was selected at the discretion of the patient's physician, prior to randomization and was administered per the physician's orders before randomization, and continued until the patient came off the randomized treatment period and entered the long-term follow-up.

Randomized treatment
"Randomized treatment" in this study refers to ^{177}Lu-PSMA-617+BSC/BSoC (investigational arm) and BSC/BSoC only (control arm).
Patients randomized to the investigational arm began ^{177}Lu-PSMA-617 administration within 28 days after randomization (C1D1). These patients received 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (±1 week) for a maximum of 6 cycles while receiving BSC/BSoC.
After Cycle 4 treatment and prior to Cycle 5 treatment, the Investigator had to determine whether:

- The patient showed evidence of response (i.e. radiological, PSA, clinical benefit)
- The patient had signs of residual disease on Computed tomography (CT) with contrast/ Magnetic resonance imaging (MRI) or bone scan
- The patient had shown good tolerance to the ^{177}Lu-PSMA-617 treatment.

If the patient met all of the criteria above and agreed to continue with additional treatment of ^{177}Lu-PSMA-617, the Investigator could administer 2 additional cycles. A maximum of 6 cycles of ^{177}Lu-PSMA-617 was allowed. If the patient did not meet any of the criteria or did not agree to additional ^{177}Lu-PSMA-617 treatment, then no additional doses of ^{177}Lu-PSMA-617 were administered after Cycle 4. After the last cycle of ^{177}Lu-PSMA-617, patients continued to be treated with BSC/BSoC as long as the investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on this study.

For both treatment arms, the cycle duration for Cycle 1-6 was 6 weeks and for Cycle 7 and beyond, was 12 weeks. From Cycle 7 onwards, all patients from both treatment arms should only be receiving BSC/BSoC.

Trial location
This study randomized 831 patients (551 assigned to ^{177}Lu-PSMA-617+BSC/BSoC arm; 280 to BSC/BSoC only arm) involving 82 sites across 8 countries in North America and Europe; 45 of the 82 sites were in the US; however, this does not raise issues with respect to applicability of the results to the US populations. The sub-study was conducted in Germany at 4 sites.

Choice of control group
BSC/BSoC as standard therapy for patients with mCRPC was chosen. The care of cancer patients included cancer specialists accomplished in the care of patients with advanced PC (e.g., medical, radiation oncologists) with a clear understanding of the PCWG3 2+2 rules for progression, management of AEs related to the natural course of the disease, as well as pre-existing AEs and study-related AEs.

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

1. Variability in global prescribing patterns and availability of different agents (to ensure the study could be international in scope)
2. The desire to provide good palliation and BSC/BSoC (since it is unethical to utilize a placebo in this population)
3. The concern that some investigators would not randomize patients to a control arm if access to an AR pathway inhibitor (as example enzalutamide or abiraterone acetate) was not allowed.

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

Diagnosis and key inclusion/exclusion criteria

Adult male patients who had a histological, pathological, and/or cytological confirmation of PC, progressive mCRPC (based on any one of the following as defined by the prostate cancer clinical trials working group 3 (PCWG3) criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease), had received at least NAAD, were previously treated with at least 1 but no more than 2 prior taxane regimens and had a positive ^{68}Ga-PSMA-11 PET/CT scan, as determined by the Sponsor's central reader. Patients treated with only 1 prior taxane-based chemotherapy regimen were eligible if the patient was unwilling to receive a second taxane regimen or the patient's physician deemed this unsuitable. Previous treatment options also included other chemotherapies or radiotherapy (such as ^{223}Ra dichloride).

Patients with previous treatment with any of the following within 6 months of randomization: strontium-89, samarium-153, rhenium-186, rhenium-188, radium-223, or hemi-body irradiation or previously treated with PSMA-targeted targeted radioligand therapy (RLT), or any systemic anti-cancer therapy (e.g. chemotherapy, immunotherapy or biological therapy) within 28 days prior to day of randomization were excluded.

Dose selection
Details are provided in Section 6.2.2.

^{68}Ga-PSMA-11
A dose range of 111-185 MBq (3-5 mCi) was used in this study. This administration of radioactivity lies within the 1.8-2.2 MBq/kg range recommended by SNMMI and EANM (Fendler et al 2017).

^{177}Lu-PSMA-617
A dose of 7.4 GBq ^{177}Lu-PSMA-617 administered once every 6 weeks for a maximum of 6 cycles has been used, for a cumulative dose of 44.4 GBq. Details are provided in Section 6.2.2.

Study treatments, treatment assignment, and blinding
The study was open-label. However, access to patient randomized treatment allocation was limited to those individuals whose roles required access to perform their study responsibilities. Details of what roles and which individuals had access to unblinded data was documented in a separate Data Access Plan maintained by the Sponsor. Date of access and reason for access were recorded.

Patients randomized to the treatment arm received BSC/BSoC and 7.4 GBq (±10%) ^{177}Lu-PSMA-617 once every 6 weeks (± 1 week) for a total of 6 doses.

The determination of the optimal dose and dose regimen was guided by efficacy and safety considerations, with an accounting for the life-threatening nature of the disease. BSC/BSoC for each patient was selected and optimized at the discretion of the patient's physician prior to randomization, and was administered as per the physician's discretion and protocol at the institution. BSC/BSoC therapy was broad but excluded investigational agents, cytotoxic chemotherapy, immunotherapy, other systemic radio isotopes (e.g. Ra-223), or hemi-body radiotherapy treatments. Details are provided in "**Choice of Control group**" above.

Shortly after commencement of the trial, a high rate of withdrawal of consent in the BSC/BSoC only arm became evident with the majority of these dropouts withdrawing consent to follow-up. This meant that radiographic progression-free survival (rPFS) data could not be collected for these patients, which consequently could result in bias in the analysis of rPFS. Enhanced study site education measures to curtail this phenomenon were implemented and made effective on 05-Mar-2019. As part of the plan to address the high rate of early withdrawal of consent in the BSC/BSoC only arm, the primary analysis of rPFS was altered to focus on patients prospectively randomized on or after 05-Mar-2019; therefore, rPFS was analyzed on an intent-to-treat (ITT) basis in these patients. The OS analysis was also planned on an ITT basis and included all randomized patients (i.e. including those randomized before 05-Mar-2019).

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

Dose modification, dose discontinuation

At the discretion of the Investigator, ^{177}Lu-PSMA-617 could be delayed or reduced with only one reduction (by 20%) allowed. Once a dose was reduced, ^{177}Lu-PSMA-617 dose could not be re-escalated. If a patient had further toxicity that required an additional reduction in administered activity, treatment with ^{177}Lu-PSMA-617 was discontinued. If a treatment delay due to adverse event (AE) or toxicity management persisted for > 4 weeks, treatment with ^{177}Lu-PSMA-617 was discontinued.

If treatment with ^{177}Lu-PSMA-617 was discontinued due to an AE, abnormal laboratory value, or toxicity, patients continued to receive BSC/BSoC only as long as the investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on this study.

Administrative structure

The study was started by Endocyte which was then acquired by Novartis. Endocyte is currently a part of AAA, which is another Novartis company. Endocyte, AAA, and Novartis staff analyzed this study and authored the reports. Trial oversight was managed by:

- A Study Steering Committee, consisting of selected investigators and Sponsor representatives, ensuring management of the study in accordance with the protocol.
- An external independent data monitoring committee (IDMC) safeguarded patient interest in the study. The IDMC included 2 oncologists, 1 nuclear medicine expert and one biostatistician. The IDMC was responsible for reviewing the safety and efficacy results, overseeing the safety data accruing in the trial at regular intervals of approximately 3 months. An independent statistical group external to Endocyte/Novartis, and not involved in the conduct of the study, prepared semi-blinded data statistical reports for the IDMC.

Assessment of imaging data for the applicable primary/secondary endpoints involved a blinded independent central review (BICR), conducted by two radiologists with a third adjudicator for discordant assessments. Imaging data used for local tumor assessment was transmitted to a designated CRO for centralized analysis, quality control, as well as further processing and data reconciliation.

Procedures and schedule

Radiographic imaging for tumor assessments: images were evaluated in accordance with both RECIST 1.1 and PCWG3 criteria. Periodic radiographic imaging included both:

- CT with contrast/MRI: CT with contrast/MRI tumor assessments included evaluations of the chest, abdomen, and pelvis.

The responses of soft tissue, lymph node, and visceral lesions to treatment were characterized using the RECIST v1.1 criteria with caveats outlined in the PCWG3 recommendations.

- Bone scans with ^{99m}Tc labeled diphosphonates: Disease progression by bone scan was characterized using the PCWG3 criteria for bone lesions.

Radiographic Imaging (CT and/or MRI and bone scan) for response evaluation was performed within 28 days prior to C1D1, every 8 weeks (±4 days) after first dose of ^{177}Lu-PSMA-617 for the first 24 weeks (independent of dose delays), then every 12 weeks until disease progression/withdrawal for any other reason. An imaging contract research organization was responsible for the collection, quality control, archival, and blinded independent central review of imaging for the study. The results of the central evaluations were used for the analysis of rPFS and overall response rate (ORR). The local Investigator's assessment was used for patient management, and was also utilized in sensitivity analyses.

Survival: all patients who consented to be in the long-term follow-up were to be followed for OS status every 3 ±1 months regardless of randomized treatment discontinuation reason.
Symptomatic skeletal events (SSE): the time to the first SSE measured the time from randomization to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurred first.
ECOG performance status: the ECOG Performance Status scale was used to assess patients' ability to perform daily living tasks and their range of basic physical ability.
Patient-reported outcomes: The Brief Pain Inventory – Short Form (BPI-SF) was used to assess the severity of pain and the impact of pain on daily functions. The FACT-P questionnaire was administered to specifically assess the HR QoL of PC patients. The FACT-P is made up of 2 parts: the FACT-G questionnaire with 27 questions, and the PCS comprising an additional 12 questions. The PCS is designed specifically to measure PC-specific quality of life. The EQ-5D-5L questionnaire was administered to assess a patient's self-reported health status.

Clinical progression: Clinical progression was assessed by the Investigator. The following criteria were used to determine when a patient had met the standard for unequivocal evidence of clinical progression:

- Marked escalation in cancer-related pain that was assessed by the Investigator to indicate the need for other systemic chemotherapy
- Immediate need for initiation of new anticancer treatment, surgical, or radiological intervention for complications due to tumor progression even in the absence of radiological progression
- Marked deterioration in ECOG performance status score to ≥ 3 and a finding of the Investigator that the deterioration indicated clinical progression

In the opinion of the Investigator, it was in the best interest of the patient to discontinue randomized treatment due to clinical progression
Biochemical responses: PSA, LDH and alkaline phosphatase (ALP) levels were measured by the local laboratory. Changes in PSA levels were used to assess PSA responses as per PCWG3 criteria.
Safety assessments made systematically during the study included monitoring of AEs and serious adverse events (SAEs), blood chemistry, hematology and urine laboratory tests, and vital signs, and pregnancies of partners. All AEs and SAEs (per NCI CTCAE v5.0) were recorded continuously until 30 days after the last dose of randomized treatment or the date of BSC/BSoC end of treatment decision, whichever is later. For patients not randomized, AE monitoring continued up to and including 6 days after administration of ^{68}Ga-PSMA-11. Patients were also assessed by the investigator after 4 cycles of ^{177}Lu-PSMA-617 for tolerance to treatment, evidence of response, and residual disease. Should the patients meet all criteria and agree to continue with additional treatment, then they proceeded to

receive two additional cycles. All patients were observed closely for short- and long-term hematological and renal toxicity regardless of the number of cycles they received.
For details on Concurrent medications, treatment compliance and rescue medications please refer to section "Treatment compliance, concomitant medications, and rescue medication use".

Subject completion, discontinuation, or withdrawal
Subjects were to be treated until confirmation of radiographic disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, death, discontinuation from the study treatment due to any other reason, or a determination by the Investigator that the patient was not clinically benefiting.

End of treatment
The end of treatment (EOT) visit was scheduled approximately 30 days after the last dose of ^{177}Lu-PSMA-617 or the date of the BSC/BSoC EOT decision (whichever occurred later), but before the initiation of subsequent anti-cancer treatment, outside of what was allowed on study. Once a patient discontinued the randomized treatment part of the study for any reason, an EOT visit was scheduled.

Withdrawal of consent
If a patient discontinued randomized treatment for any reason other than radiographic progression, they were asked for permission to continue collecting radiographic images (bone scans and CT scans and/or MRIs) for the purpose of continuing to assess rPFS. All patients who consented to be in the long-term follow-up were to be followed for OS status every 3 months (±1 month) regardless of randomized treatment discontinuation reason. Where allowed by country regulations and ECs/IRBs, patients who withdrew consent were able to be followed for overal survival via public registries. This was specified in the site specific informed consent.

End of trial
The trial and long-term follow-up procedures were expected to continue at least until 508 deaths had occurred.

Long-term follow-up
Patients who consented to be followed for long-term status updates, entered the long-term follow-up period after the EOT visit. The long-term follow-up included the collection of radiographic images (if a patient discontinued for reasons other than radiographic progression), OS, information about new treatments along with the patient's response to these treatments, AE assessment, and results of hematology and chemistry testing. During the follow-up, patients were contacted every 3 months (±1 month) via phone, email, or

letter until the end of long-term the follow-up period (24 months after the first patient enters long-term follow-up) or until 508 deaths had occurred.
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.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the description of the trial design and features of VISION. The FDA also agrees with the Applicant's description of safety assessments, follow up parameters, and characterization of the efficacy endpoints.

The following key aspects of the trial design and conduct were noted during FDA review and are discussed further in various parts of this review:

1. In VISION, 1179 patients were screened and 1003 patients had a PSMA PET-CT, of which 87% met PSMA criteria:
    - 3% did not have any PSMA-positive lesion
    - 9% were excluded because of having one PSMA negative lesion meeting the size criteria.
    - 869 (87%) patients had >=1 positive lesion and no negative lesion.
    - 831 (83%) met the rest of eligibility criteria and were randomized.
2. Best supportive care options were broad and included AR inhibitors (e.g. abiraterone, enzalutamide). Receipt of an AR agent was a stratification factor, which mitigates the risk of an imbalance between arms in receipt of AR drugs. Other key therapeutics that may confound interpretation of trial results such as cytotoxic chemotherapy, immunotherapy, other systemic radio-isotopies, or hemi-body radiotherapy were excluded on VISION.
3. After the last cycle of ^{177}Lu-PSMA-617, patients could continue to be treated with BSC/BSoC if the investigator felt they were clinically benefiting (regardless of radiographic progressive disease based on Investigator's assessment per PCWG3 criteria) or until they required a treatment regimen not allowed on this study. Any imbalance between arms in patients who continued BSC beyond progressive disease can potentially confound trial results. This is further discussed below.
4. Patients receiving ^{177}Lu-PSMA-617 were scheduled to receive 4 cycles of treatment, with an additional 2 cycles being administered if certain criteria as assessed by investigators were met.
5. VISION was an international trial but all sites were in North Ameirca and Europe and 552 (66%) of 831 patients in FAS were from the U.S. The patient population evaluated in VISION is acceptable to allow applicability of the data to a U.S. patient population.
6. VISION was an open-label trial. Given the administration of ^{177}Lu-PSMA-617, a blinded

study design may not have been feasible. Open-label trial designs can lead to bias when evaluating certain endpoints (e.g. endpoints evaluation progression or disease recurrence), however overall survival is an objective endpoint that is not subject to this bias.

7. A high rate of dropout was noted on VISION during the trial, and the Applicant met with the FDA in 2019 to discuss this issue and its impact on trial conduct. This resulted in a change to the analysis of the endpoints in VISION and is discussed further below.
8. The results of blinded independent central radiologic evaluations were used for the analysis of rPFS and overall response rate (ORR). The local Investigator's assessment was used for patient management, and was also utilized in sensitivity analyses.
9. In VISION, eligible patients were required to have PSMA-positive mCRPC defined as having at least one tumor lesion with gallium Ga 68 gozetotide uptake greater than normal liver. Patients were excluded if any lesions exceeding size criteria in short axis [organs > 1 cm, lymph nodes > 2.5 cm, bones (soft tissue component) > 1 cm] had uptake less than or equal to uptake in normal liver. ^{68}Ga PSMA-11 is a radioactive diagnostic agent which has been previously approved by FDA for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer:

    - with suspected metastasis who are candidates for initial definitive therapy.
    - with suspected recurrence based on elevated serum PSA level.

    Premarket approval application NDA 215841 for 68Ga PSMA-11 for evaluation as a companion diagnostic along with this NDA submission was submitted to CDER for the following new indication: "^{68}Ga PSMA-11 is a radioactive diagnostic agent indicated for positron emission tomography (PET) of PSMA-positive lesions in men with prostate cancer, for selection identification of patients with metastatic prostate cancer, for whom Lu 17 vipivotide tetraxetan PSMA-directed targeted therapy is indicated".

Study Endpoints

Alternate primary endpoints:
The primary objective of this study utilized two alternate primary endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received ^{177}Lu-PSMA-617 plus BSC/BSoC compared with patients who received BSC/BSoC only.

rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on blinded independent central review assessment per the PCWG3 criteria or death due to any cause. Patients who were alive without radiographic

progression at the analysis data cut-off were censored for rPFS at the time of their last evaluable radiographic assessment. The null hypothesis for rPFS, assumed the median rPFS was 4 months on BSC/BSoC only treatment for a HR of 1.00. Under the alternative hypothesis, median rPFS on 177Lu-PSMA-617+BSC/BSoC treatment was assumed to be 6 months for a HR of 0.67.
The null hypothesis, was tested at a one-sided level of significance. The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The primary analysis of rPFS was based on the PFS-FAS population. The rPFS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including number at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 99.2% CIs are presented for each treatment arm. The rPFS Kaplan-Meier estimate along with 99.2% CIs are presented at different time points (e.g. 3, 6, and 12 months) for each treatment arm. The one-sided p-value from the log-rank test is presented.

OS was defined as the time (in months) from the date of randomization to the date of death due to any cause. If the patient was not known to have died, then OS was censored. The censoring date was date of the last contact, until the cut-off date. The cut-off date was not used for last contact date, unless the patient was seen or contacted on that date. The null hypothesis for survival, assumed median OS was 10 months on BSC/BSoC only treatment for a HR of 1.00. Under the alternative hypothesis, median OS on ^{177}Lu-PSMA-617+BSC/BSoC treatment was assumed to be 13.7 months for a HR of 0.7306. The null hypothesis was tested at a one-sided level of significance. The primary analysis was to test the null hypothesis and compare the two treatment arms using a stratified log-rank test stratifying for the randomization stratification factors. The primary analysis of OS was based on the FAS population. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves (including numbers at risk and confidence limits), median, 25th percentile, and 75th percentile and associated 95% CIs are presented for each treatment arm. The OS Kaplan-Meier estimate along with 95% CIs are presented at different time points (e.g. 6, 12, and 18 months) for each treatment arm. The one-sided p-value from the log-rank test is presented.

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

The Applicant's Position:

Overall, the study design allowed the appropriate assessment of the efficacy and safety of ^{177}Lu-PSMA-617.

The FDA's Assessment:
FDA agrees with the Applicant's position, however, our standard approach is to use 95% confidence intervals rather than 99.2% confidence intervals. FDA will report 95% confidence intervals in the assessment aid and the label.

FDA notes that rPFS is a tumor-based endpoint that uses bone scan assessments which may instill more variability into the precision of estimating the delay in tumor progression. The clinical meaningfulness of rPFS therefore relies on a large magnitude of effect.

Statistical Analysis Plan and Amendments

Applicant Position:
The statistical analysis plan (SAP) was agreed upon and finalized prior to the conduct of any efficacy analysis and unblinding of the database.

Efficacy analysis
The primary analysis of rPFS was based on the blinded independent central radiological assessment. The FAS comprised all subjects who were randomized to study treatment and the PFS-FAS comprised all subjects who were randomized to study treatment on or after 5-Mar-2019. According to the intent to treat principle, subjects were analyzed according to the treatment, and strata they were assigned to during the randomization procedure. The FAS and PFS-FAS were the main population for analyses of subject disposition, demographics, baseline characteristics, and efficacy analyses of the alternate primary endpoints.
Rules for the handling of missing data were specified in the SAP to ensure overall data integrity. Sensitivity analyses (for handling missing tumor assessments) and supportive analyses (including local radiological assessment) were performed to assess the overall robustness of the primary efficacy results. Subgroup analyses based on important demographic and prognostic factors to explore the intrinsic consistency of any treatment effect in the overall population of subjects were prespecified in the SAP.

The primary efficacy analyses were the comparison of the distribution of rPFS between the two treatment groups using a stratified log-rank test at a one-sided 0.4% level of significance in the PFS-FAS and the comparison of the distribution of OS between the two treatment groups using a stratified log-rank test at a one-sided level of significance in the FAS depending on the results of rPFS (either a one-sided 2.5% level of significance if rPFS stratified log-rank test p-value<0.004 or a one-sided 2.1% level of significance if rPFS stratified log-rank test p-

value>0.004). Alpha allocation and recycling was used to address multiplicity and control the overall type-I error rate. A maximum of two analyses was planned; a final analysis of rPFS with an interim analysis of OS after observing approximately 364 rPFS events and a final OS analysis after approximately 508 events.

The analyses of the three key secondary efficacy endpoints were the comparisons of ORR and DCR between the two treatment groups in the Response evaluable analysis set (a subset of the PFS-FAS with RECIST evaluable disease at baseline) and the distribution of time to first SSE between the two treatment groups in the PFS-FAS. The Hochberg closed test procedure was used to control the overall type-I error rate, where the key secondary efficacy endpoints were to be statistically evaluated and interpreted only if OS was statistically significant. ORR and DCR between the two treatment arms were compared using the Wald's chi-square test from the stratified logistic regression model (strata based on the randomization stratification factor) and the distribution of time to first SSE between the two treatment arms was compared using a stratified log-rank test. The key secondary efficacy endpoints were compared using either a two-sided 5.0% level of significance if the OS stratified log-rank test p-value<0.025 or a two-sided 4.2% level of significance if OS stratified log-rank test p-value<0.021).

The statistical plan was amended two times during the study to reflect changes in protocol design (see Section "Protocol Amendments"). Key changes included the following:

Version 2.0 (24-Oct-2019)
Updated analysis set to use for the primary analysis comparison of rPFS, time to first SSE and other secondary efficacy endpoints to the PFS-FAS (subjects randomized on or after 5-Mar-2019).
Added analyses pertaining to the secondary objectives of the sub-study.
Clarified that the strata based on the randomization stratification factors during the randomization procedure would be used for all efficacy analyses.
Changed the statistical test to compare the primary endpoints (rPFS and OS) from the Wald chi-square test from the stratified Cox regression model to the stratified log-rank test (strata based on randomization stratification factors).
Subgroup analyses for the primary endpoints of rPFS and OS, by (i) baseline LDH, (ii) presence of liver metastases at baseline, (iii) ECOG score at baseline, (iv) age and (ii) race were added.
Added supportive analyses for rPFS including (i) describing subjects randomized prior to 5-Mar-2019 and withdrew consent as rPFS event or censored at the time of withdrawal and (ii) analysis of missing and timing of tumor assessments.
Clarified level of significance to use for testing the key secondary efficacy endpoints.

Version 3.0 (18-Jan-2021)

Changed the statistical test to compare the key secondary efficacy endpoint, time to first SSE from the Wald chi-square test from the stratified Cox regression model to the stratified log-rank test (strata based on randomization stratification factors).
Clarified that if interim OS analysis is met, that the final OS analysis will be presented descriptively without inference.
Added the alpha level of significance to be used for the primary analysis of OS and the key secondary efficacy endpoints if the interim analysis of OS is not performed.
Added analyses for rPFS: (i) based on local radiological assessment, (ii) concordance between BICR and local assessment and (iii) modified the analysis of missing and timing of tumor assessments.
Added analysis of OS in the PFS-FAS (subjects randomized on or after 5-Mar-2019).
Added analyses to describe and assess the impact of COVID-19 including (i) sensitivity analyses for rPFS and OS, (ii) protocol deviations due to COVID-19 and (iii) COVID-19 related AEs.

Safety analysis
All safety analyses related to randomized treatment were based on the FAS safety analysis set which consisted of all subjects who received at least one dose of the randomized treatment. Subject data were analyzed according to the treatment actually received. Separate AE summaries were presented by system organ class, preferred term, and maximum CTC grade. All AEs, grade 3-4 AEs, treatment-related AEs, SAEs, AEs leading to discontinuation, AEs requiring dose reduction or interruption, safety topics of interest (including adverse events of special interest (AESI)), and the number (%) of subjects with worst post-baseline laboratory data, clinically notable vital sign abnormalities, and notable ECG abnormalities were summarized by treatment group. Safety summary tables included "on-treatment" events/assessments, i.e. those collected on or after the first date of randomized treatment and collected no later than 30 days after the date of last randomized treatment administration. AE summaries and worst post-baseline laboratory data during long-term follow-up were presented separately.

The FDA's Assessment:
The analysis plan for OS and rPFS per BICR are acceptable. The Hochberg closed test procedure was used to control the overall Type I error rate. There was one interim analysis for OS performed at the final rPFS analysis. The interim OS analysis was not completed as the targeted number of OS events for the final analysis were observed before the targeted number of rPFS events. The OS analysis was based on all randomized patients on an ITT basis (FAS), while the rPFS analysis was based on a smaller number of randomized patients enrolled on or after March 5, 2019 (PFS-FAS).

Protocol Amendments

The study protocol was amended 9 times prior to database lock for the clinical study report: 3 global amendments and 5 country specific amendments (1 for UK, 2 for Sweden and 2 for

Germany). The clinical study report describes the study conduct as amended in Protocol Version 4.0. A detailed discussion of amendments that had an impact on the interpretation of study results is provided below the table.

Originally the primary objective of this study was an arm-to-arm comparison of OS. Hence, the study was designed to randomize 750 patients, with 2 formal interim efficacy analyses planned at 50% and 70% of the total planned number of OS events (489 deaths). rPFS was a key secondary endpoint. The changes of each amendment are summarized in Table 14.

Table 14: Protocol amendments

Version No. (Date)	Summary of changes
1.1 (03-Jul-2018) Approved by IEC/IRB	Amendment specific for Great Britain only: • AE assessment timing to start from consent. • Added wording regarding birth control.
1.2 (26-Sep-2018) Approved by IEC/IRB	Amendment specific for Germany only: • AE assessment timing to start from consent. • Added wording regarding birth control.
2.0 (16-Jan-2019) Sites never operated using this amendment. It was provided to some IECs in order to have Amendment 3.0 approved	• Incorporated GB and DE only amendment changes. • Added statement of compliance as required by Sweden. • Incorporated the addition of the alternate primary endpoint of rPFS and updated to 1 rPFS analysis and 1 OS analysis. • Clarified inclusion of and timing of start for BSC/BSoC. • Clarified inclusion/exclusion criteria. • Clarified procedures and timing. • Clarified progression of disease is not considered as an AE or SAE. • Clarified start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and BSC/BSoC dosing and intervention TEAEs.
3.0 (01-Apr-2019) Approved by IEC/IRB	• Updated Sponsor name. • Updated background information data. • Clarified rPFS is an alternate primary endpoint. • Clarified inclusion/exclusion criteria and added specific criteria regarding BSC/BSoC options to be identified for patients as part of eligibility. • After Cycle 6, visits are now every 12 weeks (±4 days). • Additional details regarding long-term follow-up were added including a second consent to be signed by patients who withdraw consent or leave the active part of the study for any reason other than radiographic disease progression. This included radiographic follow-up. • Plasma testosterone was added as an acceptable form of testosterone testing. • Window for QoL and Pain questionnaires added.

Version No. (Date)	Summary of changes
	• Updated reference section.
4.0 (08-Jul-2019) Approved by IEC/IRB	• Increased total number of patients randomized in the study by 64 to ensure sufficient events in order to maintain power for total enrollment of 814 patients. • Details for confirmatory analysis of OS (based on all randomized patients on an Intent to Treat (ITT) basis i.e., all patients enrolled since the start of the study) and the rPFS analysis based on randomized patients on or after 5-Mar-2019 were added. • Adjusted the allocation of alpha between rPFS and OS while still maintaining the original power for both rPFS (approximately 85%) and OS (90%). Allocated alpha=0.004 to rPFS, 0.001 to interim OS and alpha of 0.02 to 0.025 for OS. Previously, allocation was rPFS=0.001 and OS=0.023. • Additional imaging analyses details were added for ^{68}Ga-PSMA-11 scan data and the role of the Independent Review with reviewer variability assessment, as well as Quantitative Analysis was added to assess tumor burden and tumor characteristics with rPFS, OS, and other response measures, as determined by PCWG3 criteria. • Further clarification on the start and end timing for ^{68}Ga-PSMA-11 TEAEs, ^{177}Lu-PSMA-617 TEAEs and BSC/BSoC dosing and intervention TEAEs. • Additional wording to clarify intent to collect radiographic imaging for patients who stopped treatment for reasons other than radiographic progression.
4.1 (09-Aug-2019) Approved by IEC/IRB	Amendment specific for Germany only: • All protocol changes noted above for Versions 2, 3 and 4 were included. • Added a dosimetry, PK and ECG sub-study which included a non-randomized cohort (^{177}Lu-PSMA-617+BSC/BSoC) of approximately 30 patients from selected sites in Germany.
4.2 (25-Feb-2020) Approved by IEC/IRB	Amendment specific to Sweden only: • Updates to sections regarding LTFU, removing requirement to sign additional consent at end of treatment

4.3 (04-Jun-2020)
Approved by IEC/IRB
	Amendment specific to Sweden only:
	• Updated Medical Officer email address
	• Minor updates after review by the country investigator to the following sections to provide further clarity in regards to end/completion of treatment and withdrawal of consent:
	  ◦ Clinical Trial Summary
	  ◦ 3.1 Overview of the Clinical Trial Study design
	  ◦ 3.4.4 End of Treatment Visit
	  ◦ 4.3 Subject Withdrawal of Consent for Study or Treatment
	  ◦ 5.5 Treatment discontinuation

4.4 DE (22-Jul-2020)	Amendment specific to Germany only:

Version No. (Date)	Summary of changes
Approved by IEC/IRB	• Additional imaging procedures of whole body planar and 3D SPECT from cycle 2 through cycle 6 of PSMA-617 treatment to align and comply with local radioprotection laws and established guidelines in Germany. • Implementation of estimated glomerular filtration rate (eGFR) from cycle 1 through cycle 6 of PSMA-617 treatment to further assess potential renal toxicity.

The FDA's Assessment:

FDA agrees with the description of protocol amendments. Originally, the primary endpoint was OS, 750 patients was the targeted sample size, there were 2 formal interim analyses, and rPFS was a key secondary endpoint. rPFS was added as a co-primary endpoint in addition to OS shortly after the first patient visit.

The Applicant met with the FDA to discuss considerable withdrawal of consent and disproportionate drop-out in the ^{177}Lu-PSMA-617 arm in VISION. The Applicant reported that of the 300 patients randomized as of March 22, 2019, 69 patients had withdrawn consent <8 weeks after randomization (before the first post-baseline radiologic assessment). Fourteen (7%) of these patients were in the experimental arm and 55 (53%) were in the control arm. The Applicant attributed the disproportionality to the non-blinded trial design and public information on the potential efficacy of the study drug contributing to withdrawal consent. Specifically, the Applicant noted that after discussion with site investigators, many patients were disappointed or angry when they were not randomized to the study drug, wanted other therapies such as taxanes (which were not allowed), or were not willing to comply with the visit schedule in the protocol.

The Applicant implemented corrective actions in February 2019 that included site calls to discuss management of control arm patients, investigator letters clarifying study aspects, updates to pre-screening to educate patients better, etc. After implementation of these measures, the Applicant noted that withdrawal of consent decreased considerably, and the Applicant subsequently submitted a protocol amendment that included measures to support enrollment of appropriate patients on study.

Due to the high early dropout rate among the BSC arm, the total number of patients was increased to 814 patients. Subsequently, rPFS was only prospectively analyzed in patients randomized after these measures were implemented. The PFS-FAS analysis was instituted to mitigate bias in the analysis of rPFS because rPFS data could not be collected for the patients with early dropout. OS was still analyzed in all randomized patients. FDA found this approach to be acceptable. Further discussion on evaluation of early dropout rates can be found in Section 8.

The allocation of alpha between rPFS and OS was adjusted while still maintaining the original power for both rPFS (approximately 85%) and OS (90%), with alpha=0.004 allocated to rPFS and 0.001 to interim OS, and alpha of 0.02 to 0.025 for OS (previously, allocation was rPFS=0.001 and OS=0.023).

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:
The studies were conducted in full conformance with the ethical principles of good clinical practice (GCP) and the Declaration of Helsinki. Written informed consent was obtained from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB).
Informed consent was obtained in writing from each subject or legally acceptable representative of the subject, before conducting any study-specific procedures. The study was described by the Investigator or designee, who answered any questions, and written information was also provided.

The FDA's Assessment: Four clinical investigators (CI), Drs. Michael Morris (Site 100104), Nitin Vaishampayan (Site 100029), Scott Tagawa (Site 100152), and Edward Gelmann (Site 100006) and the sponsor (Endocyte, Inc., A Novartis Company) were selected for Good Clinical Practice (GCP) inspections. Inspections of the four CIs and the study sponsor found no significant regulatory deficiencies. The Applicant's submitted clinical data, including the reported patient PSMA eligibility per the sponsor's prespecified criteria and determination, were verifiable against source records at the sites. Based on the results of these inspections, Study PSMA-617-01 appears to have been conducted adequately, and the clinical data generated by these four CI sites appear reliable and acceptable for this NDA.

Financial Disclosure

The Applicant's Position:
Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. No disclosed interests/arrangements raise questions about the integrity of the data.

For Study PSMA-617-01:
No conerns are raised at this time given that the study design minimizes potential bias because it was:

- international, across 9 countries,
- randomized,
- contained objective endpoints (rPFS, one of the alternate primary endpoints was based on central blinded reads).

An independent Data Monitoring Committee (IDMC) was also in place and reviewed safety and efficacy data during the course of the study.

Additionally no site with investigators who disclosed financial interests/arrangments enrolled more than 3% of total randomized patients. The two sites with the highest enrollment within this group were audited by the Sponsor. No issues regarding financial bias were found.

These issues do not affect the review, or the approvability of the application. Details of financial disclosure are presented in Section 19.2.

For study PSMA-617-02:
No conerns are raised at this time. The protocol design minimized potential bias because it was randomized. Of note, enrollment was ended early as previously stated and efficacy was no longer able to be assessed.

An independent data monitoring committee was set up for review of patient data and increased monitoring and data review was performed by the CRO as well as additional Sponsor representatives (CRA) once the study transitioned to Endocyte, Inc.

These issues do not affect the review, or the approvability of the application. Details of financial disclosure are presented in Section 19.2.

The FDA's Assessment:
FDA agrees with the Applicant's position that the randomized design in VISION (Study PSMA-617-01) and stratification of randomization by LDH, ECOG PS, presence of liver metastasis, and use of androgen receptor inhibitors reduced the bias by increasing the balance in patients characteristics between treatment arms.

Patient Disposition

The Applicant's Position:
PSMA-617-01:

Screened: 1179 patients were assessed for eligibility (signed an informed consent). 176 patients were excluded from undergoing a ^{68}Ga-PSMA-11 PET/CT scan, mainly because they failed to meet eligibility criteria prior to imaging (N=141) or had withdrawn their consent (N=24).

PSMA-11 Safety Analysis Set: All patients who received a dose of ^{68}Ga-PSMA-11. This included screened patients who were not randomized. 1003 patients underwent a ^{68}Ga-PSMA-11 PET/CT scan; 172 were excluded from randomized treatment, mainly because

they failed to meet eligibility criteria for randomization (N=164, including 123 patients with negative ^{68}Ga-PSMA-11 PET/CT scan per the exclusionary read rules).
Full Analysis Set (FAS): FAS consisted of all randomized patients. 831 patients were randomized to either ^{177}Lu-PSMA-617+BSC/BSoC arm (N=551) or BSC/BSoC only arm (N=280).
PFS full analysis set (PFS-FAS): 581 patients were randomized on or after 05-Mar-2019 to either ^{177}Lu-PSMA-617+BSC/BSoC arm (N=385) or BSC/BSoC only arm (N=196).
Response evaluable analysis set: 439 patients were randomized on or after 05-Mar-2019 to either ^{177}Lu-PSMA-617+BSC/BSoC arm (N=319) or BSC/BSoC only arm (N=120), a subset of patients with RECIST evaluable disease at baseline.
FAS safety analysis set: 734 patients were treated with ^{177}Lu-PSMA-617+BSC/BSoC arm (N=529) or BSC/BSoC only arm (N=205). See Table 15 for additional information.

Table 15: Randomized Patient Disposition in PSMA-617-01 (FAS)

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	^{177}Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Patients treated	533 (96.7)	201 (71.8)	734 (88.3)
Patients not treated [1]	18 (3.3)	79 (28.2)	97 (11.7)
Patients still on treatment [2]	49 (8.9)	5 (1.8)	54 (6.5)
Patients who discontinued from all study treatments	484 (87.8)	196 (70.0)	680 (81.8)
Patients treated with ^{177}Lu-PSMA-617	**529 (96.0)**		
Patients not treated with ^{177}Lu-PSMA-617	22 (4.0)		
Reason not treated with ^{177}Lu-PSMA-617			
Adverse event	6 (1.1)		
Investigator decision	3 (0.5)		
No longer clinically benefitting	3 (0.5)		
Withdrew consent (treatment)	3 (0.5)		
Death	2 (0.4)		
Other	2 (0.4)		
Protocol deviation	2 (0.4)		
Progressive disease	1 (0.2)		
Patients who completed ^{177}Lu-PSMA-617 [5]	250 (45.4)		
Patients who discontinued from ^{177}Lu-PSMA-617	279 (50.6)		
Reason for discontinuation from ^{177}Lu-PSMA-617			
Progressive disease	127 (23.0)		
Adverse event	54 (9.8)		
No longer clinically benefitting	36 (6.5)		
Withdrew consent (treatment)	23 (4.2)		
Investigator decision	16 (2.9)		
Death	14 (2.5)		
Patient requires care not allowed in the study	6 (1.1)		
Other	2 (0.4)		
Patient lost to follow-up	1 (0.2)		
Patients treated with BSC/BSoC	**533 (96.7)**	**201 (71.8)**	**734 (88.3)**
Patients not treated with BSC/BSoC	18 (3.3)	79 (28.2)	97 (11.7)
Reason not treated with BSC/BSoC			
Withdrew consent (treatment)	2 (0.4)	46 (16.4)	48 (5.8)
Patient requires care not allowed in the study	0	16 (5.7)	16 (1.9)
No longer clinically benefitting	2 (0.4)	5 (1.8)	7 (0.8)
Subject lost to follow-up	0	4 (1.4)	4 (0.5)
Death	2 (0.4)	3 (1.1)	5 (0.6)
Other	2 (0.4)	3 (1.1)	5 (0.6)
Progressive disease	1 (0.2)	1 (0.4)	2 (0.2)
Investigator decision	2 (0.4)	1 (0.4)	3 (0.4)
Adverse event	5 (0.9)	0	5 (0.6)
Protocol deviation	2 (0.4)	0	2 (0.2)
Reason for discontinuation from BSC/BSoC			
Progressive disease	224 (40.7)	73 (26.1)	297 (35.7)
No longer clinically benefitting	72 (13.1)	50 (17.9)	122 (14.7)
Withdrew consent (treatment)	51 (9.3)	36 (12.9)	87 (10.5)
Investigator decision	39 (7.1)	9 (3.2)	48 (5.8)

Adverse event	29 (5.3)	4 (1.4)	33 (4.0)
Death	26 (4.7)	8 (2.9)	34 (4.1)
Patient requires care not allowed in the study	26 (4.7)	11 (3.9)	37 (4.5)
Other	12 (2.2)	1 (0.4)	13 (1.6)
Patient non-compliance	4 (0.7)	3 (1.1)	7 (0.8)
Patient lost to follow-up	1 (0.2)	0	1 (0.1)
Protocol deviation	0	1 (0.4)	1 (0.1)
Patients continuing in long-term follow-up period [3]	**140 (25.4)**	**50 (17.9)**	**190 (22.9)**
Patients who discontinued from study	362 (65.7)	225 (80.4)	587 (70.6)
Reason for discontinuation from study			
Death	329 (59.7)	167 (59.6)	496 (59.7)
Withdrew consent (protocol) [4]	29 (5.3)	53 (18.9)	82 (9.9)
Patient lost to follow-up	4 (0.7)	4 (1.4)	8 (1.0)
Investigator decision	0	1 (0.4)	1 (0.1)

[1] Patients who did not receive ^{177}Lu-PSMA-617 nor BSC/BSoC. 4 patients randomized to ^{177}Lu-PSMA-617+BSC/BSoC did not receive ^{177}Lu-PSMA-617; they only received BSC/BSoC.
[2] Patients still on treatment at the time of the data cut-off date 27-Jan-2021
[3] Patients in long-term follow-up period are those no longer on treatment and have not discontinued from the study at the time of the data cut-off date.
[4] 34 patients who had withdrew consent (protocol) were later reported has dead through public registry search.
[5] "Completed ^{177}Lu-PSMA-617" indicates completed at least 4 cycles as reported by the investigator

Protocol Violations/Deviations

The Applicant's Position:

In the study PSMA-617-01, protocol deviations were generally more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm which could be related in part to the longer duration of exposure in this arm.

The most frequent deviations for each category were (^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm) were:

- Study procedure or assessment (23.2% vs. 15.0%): mainly missed imaging visit or assessments: 15.8% vs. 9.3%
- Inclusion/exclusion criteria (20.1% vs. 15.7%): mainly metastatic lesion evident, but not within 28 days of baseline: 12.9% vs. 11.1%
- Informed consent (8.9% vs. 9.3%): mainly significant delay in re-consenting, where consent included updates to safety: 6.2% vs. 6.4%
- Study medication (6.7% vs. 0.7%): mainly lack of adequate temperature monitoring of PSMA-11 kits: 2.4% vs. 0.7%
- Randomization procedure (5.1% vs. 2.5%): mainly incorrect stratification - inclusion of NAAD as BSC/BSoC: 2.4% vs. 0.4%

The FDA's Assessment:

FDA review further evaluated reasons for protocol deviations. The study protocol specified that only patients who had residual disease after completion of 4 doses would be considered for an additional 1-2 doses of ^{177}Lu-PSMA-617. However, FDA identified 19 patients in the ^{177}Lu-PSMA-617+BSC/BSoC arm who had a confirmed CR after completion of 4 cycles of treatment, of which 17 patients still received additional doses of ^{177}Lu-PSMA-617. These 17 patients comprised 3.2% of the 529 patients in the ^{177}Lu-PSMA-617 arm. FDA analysis determined that this did not substantially affect efficacy outcomes or affect interpretation of the reported trial results from VISION. Due to insufficient data on safety and efficacy of 4 cycles of ^{177}Lu-PSMA-617 in patients who achieved CR after 4 cycles, no conclusion could be made on adequacy of 4 cycles of treatment. The FDA's recommended duration of treatment with ^{177}Lu-PSMA-617 in label is "up to 6 doses, or until disease progression, or unacceptable toxicity".

Overall, protocol deviations observed in VISION do not appear to affect interpretation of trial results from VISION.

Demographic and Baseline Characteristics

The Applicant's Position:
Only data from the pivotal study Phase III Study PSMA-617-01 is included in this section.

In study PSMA-617-01, treatment arms were generally well balanced and represented the intended subject population with respect to demographic and baseline characteristics, thereby providing reassurance with regard to the interpretation of the treatment comparison and validity of the efficacy conclusions (FAS) (Table). Similarly, as seen with the FAS, these characteristics were also well balanced between treatment arms in the PFS-FAS and the Response evaluable analysis set.

Of note, all sites were localized in Europe or North America (USA and Canada), and therefore a majority of patients recruited were White (86.8%), 6.6% were Black or African American, and only 2.4% were Asian. As anticipated for the disease under study, a high proportion of patients were age 65 or over (75.3%).

Table 16: Demographic and baseline characteristics (FAS) in PSMA-617-01

	Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Age (years)			
n	551	280	831
Mean (SD)	69.7 (7.4)	70.5 (7.8)	70.0 (7.6)
Median	70.0	71.5	71.0

	Lu-PSMA-617 +BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Min-max	48-94	40-89	40-94
Age (categorized), n (%)			
< 65 years	145 (26.3)	60 (21.4)	205 (24.7)
≥ 65 years	406 (73.7)	220 (78.6)	626 (75.3)
≥ 65-84 years	398 (72.2)	214 (76.4)	612 (73.6)
≥ 85 years	8 (1.5)	6 (2.1)	14 (1.7)
Race, n (%)			
White	486 (88.2)	235 (83.9)	721 (86.8)
Black or African American	34 (6.2)	21 (7.5)	55 (6.6)
Asian	9 (1.6)	11 (3.9)	20 (2.4)
Other [1]	2 (0.4)	0	2 (0.2)
Missing	20 (3.6)	13 (4.6)	33 (4.0)
Ethnicity, n (%)			
Hispanic or Latino	11 (2.0)	3 (1.1)	14 (1.7)
Not Hispanic or Latino	471 (85.5)	240 (85.7)	711 (85.6)
Not reported	69 (12.5)	37 (13.2)	106 (12.8)
Weight (kg)			
n	535	272	807
Mean (SD)	88.0 (17.3)	88.1 (16.5)	88.0 (17.0)
Median	85.3	86.0	85.7
Min-max	54.0-160.0	52.3-147.0	52.3-160.0
Body mass index (kg/m^2)			
n	517	266	783
Mean (SD)	28.4 (5.1)	28.0 (4.7)	28.2 (5.0)
Median	27.7	27.4	27.7
Min-max	17.0-48.4	20.3-44.6	17.0-48.4
ECOG performance status, n (%) [2]			
0-1	510 (92.6)	258 (92.1)	768 (92.4)
2	41 (7.4)	22 (7.9)	63 (7.6)

[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.

The FDA's Assessment:

FDA agrees with the Applicant's position. Notably, Black or African American, and Asian patients were underrepresented in VISION.

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Other Baseline Characteristics (eg, baseline disease characteristics, important concomitant drugs)

The Applicant's Position:

Baseline disease characteristics for all randomized patients (the FAS) are presented in 17. These characteristics were balanced between the 2 randomized arms. The results were similar for the PFS-FAS and Response evaluable analysis set.

Table 17: Baseline disease characteristics (FAS) in PSMA-617-01

	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Time since initial cancer diagnosis (years)			
n	551	280	831
Mean (SD)	8.3 (5.5)	8.9 (5.8)	8.5 (5.6)
Median	7.4	7.4	7.4
Min-max	0.9-28.9	0.7-26.2	0.7-28.9
Initial histopathological classification, n (%)			
Adenocarcinoma	497 (90.2)	258 (92.1)	755 (90.9)
Neuroendocrine	1 (0.2)	0	1 (0.1)
Unknown	47 (8.5)	20 (7.1)	67 (8.1)
Other	6 (1.1)	2 (0.7)	8 (1.0)
Baseline target lesions, n (%)			
Yes	279 (50.6)	140 (50.0)	419 (50.4)
No	272 (49.4)	140 (50.0)	412 (49.6)
Baseline non-target lesions, n (%)			
Yes	429 (77.9)	212 (75.7)	641 (77.1)
No	122 (22.1)	68 (24.3)	190 (22.9)
Total sum of target lesion diameters (mm)			
n	279	140	419
Mean (SD)	58.5 (46.4)	58.6 (44.9)	58.5 (45.9)
Median	45.0	46.2	45.0
Min-max	10-351	10-249	10-351
Site of disease (target and non-target lesions), n (%) [1]			
Lung			
Yes	49 (8.9)	28 (10.0)	77 (9.3)
No	502 (91.1)	252 (90.0)	754 (90.7)
Liver			
Yes	63 (11.4)	38 (13.6)	101 (12.2)
No	488 (88.6)	242 (86.4)	730 (87.8)
Lymph node			
Yes	274 (49.7)	141 (50.4)	415 (49.9)
No	277 (50.3)	139 (49.6)	416 (50.1)
Bone			
Yes	504 (91.5)	256 (91.4)	760 (91.5)
No	47 (8.5)	24 (8.6)	71 (8.5)

	Lu-PSMA-617+ BSC/BSoC N=551	BSC/BSoC only N=280	Overall N=831
Baseline PSA doubling time (months) [2]			
n	269	131	400
Mean (SD)	3.2 (5.3)	4.3 (9.1)	3.6 (6.8)
Median	2.4	2.6	2.4
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	8 (3.0)	4 (3.1)	12 (3.0)
≤ 6 months	245 (91.1)	115 (87.8)	360 (90.0)
> 6 months	16 (5.9)	12 (9.2)	28 (7.0)
Baseline PSA (ng/mL)			
n	551	280	831
Mean (SD)	288.4 (675.8)	387.6 (937.0)	321.8 (774.6)
Median	77.5	74.6	76.0
Min-max	0-6988	0-8995	0-8995
Baseline ALP (IU/L)			
n	547	278	825
Mean (SD)	153.7 (183.7)	150.3 (168.1)	152.6 (178.5)
Median	105.0	94.5	101.0
Min-max	17-2524	28-1355	17-2524
Baseline LDH (IU/L)			
n	550	279	829
Mean	286.4 (283.9)	297.5 (261.7)	290.1 (276.6)
Median	221.0	224.0	223.0
Min-max	88-5387	105-2693	88-5387

[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). Patie nts with at least 3 PSA values prior to and at the time of screening were included in the model.

The FDA's Assessment: FDA agrees with the Applicant's position. FDA review also included evaluation of prior therapies received in all enrolled patients. Patients with at least 1 prior prostate cancer-related surgery (^{177}Lu-PSMA-617: 96% vs. BSC only: 97%) or cancer-related radiotherapy (^{177}Lu-PSMA-617: 75% vs. BSC only: 78%) were balanced between arms.

All patients in VISION received at least one prior cancer-related systemic therapy. The most frequent systemic therapies were therapeutics for 77% of patients and adjuvant therapies for 31% of patients. All patients received at least one prior AR inhibitor and taxane based chemotherapy.

Table 18. Selected Prior Systemic Anti-Cancer Therapies for Prostate Cancer

	177Lu-PSMA-617 +BSC/BSoC (N=551)	BSC/BSoC only (N=280)

Number of prior ARIs (%)		
1	296 (54%)	130 (46%)
≥2	255 (46%)	50 (54%)
Number of prior taxanes(≥2 cycles)		
1	342 67%	165 63%
2	170 33%	99 37%
missing	39 (7%)	16 (6%)

There was a slightly higher proportion of patients with ≥2 prior ARI therapies or 2 prior taxane therapies in BSC/BSoC only group. These minor differences do not appear to be substantial enough to affect interpretation of trial results from VISION and are generally well-balanced.

On October 27th, 2021, the Applicant submitted data on tumor characteristics on ^{68}Ga-PSMA-11 PET CT scan. Disease burden was defined as the volume of segmented PSMA positive tumor (PSMA + tumor volume) in the whole body using ^{68}Ga-PSMA-11 PET imaging. Disease burden was categorized as <median value of PSMA + tumor volume in the whole body vs ≥median value. The median PSMA + tumor volume in the whole body was derived using all patients randomized to the PLUVICTO + BSoC/BSC arm who had good quality images available. Baseline body weight was categorized as <80 kg vs. ≥80 kg. Subgroup characteristics of baseline body weight and PSMA + tumor volume in the whole body in the ^{177}Lu-PSMA-617 + BSoC/BSC arm for the FAS and PFS-FAS are presented in the table below.

Table 19. Subgroup characteristics of PSMA-positive tumor volume (cc) in whole body by baseline body weight and overall in the 177Lu-PSMA-617 + BSoC/BSC arm

	FAS (N=551)	PFS-FAS (N=385)
Tumor voume in whole body	n=548	n=382
< 398.144 cc	274 (50%)	169 (44%)
≥ 398.144 cc	274 (50%)	213 (56%)
Baseline body weight < 80 kg	n=193	n=141
< 398.144 cc	101 (52%)	67 (48%)
≥ 398.144 cc	92 (48%)	74 (52%)
Baseline body weight ≥ 80 kg	n=339	n=226
< 398.144 cc	167 (49%)	96 (42%)
≥ 398.144 cc	172 (51%)	130 (58%)

Patient characteristics by tumor volume in whole body and by baseline body weight were balanced between arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance

No formal treatment compliance measurement was performed. ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 were administered at the site, under the supervision of qualified personnel. BSC/BSoC was optimized for all study participants prior to randomization and was administered as per physician's orders and at the institution whenever feasible. BSC/BSoC compliance was not monitored and BSC/BSoC could be adapted during the study at the discretion of the investigator to the best interest of the patient.

Concomitant Medications

Overall, the proportion of subjects who required concomitant medication was similar in both treatment arms for the FAS safety analysis set and was as anticipated for a patient population with an advanced disease and a relatively long time since initial diagnosis.
Protocol deviations due to the use of prohibited concomitant medications were reported in 11/280 (3.9%) patients in the BSC/BSoC only arm, and 4/551 (0.7%) patients in the ^{177}Lu-PSMA-617.

All patients in the FAS safety analysis set (100%) received at least 1 concomitant medication. Concomitant medications were balanced between the 2 randomized arms, with differences that were typically < 10% with the exception of (^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only arm):

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

Concurrent radiotherapy

Incidence and site of radiotherapy were balanced between the 2 randomized arms. Overall, 17.8% received at least one radiotherapy, and the most frequent site of radiotherapy was the back (6.4%).

Concurrent surgical and therapeutic procedures

Concurrent surgical and therapeutic procedures were balanced between the 2 randomized arms. Overall, 22.1% had a least 1 procedure, including 11.9% who had at least 1 investigation (the most frequent was chest X-ray, 1.8%) and 15.0% who had at least 1 surgical and medical procedure (the most frequent were nephrostomy and uteral stent insertion, 1.9% each).

The FDA's Assessment: There was an imbalance between arms in terms of concomitant anti-androgen therapies received (^{177}Lu-PSMA-617 arm: 35% vs. BSC only arm: 48%). This was mostly driven by an imbalance between arms in the use of enzalutamide (30% vs. 42% in ^{177}Lu-

PSMA-617 vs. BSoC only arm, respectively).

The most common concomitant treatments used as BSC/BSoC are listed in the table below. The proportions of patients treated with enzlutamide, abiraterone, bisphosphonates, glucocorticoids, and/or radiation therapy was higher in BSC/BSoC only group.

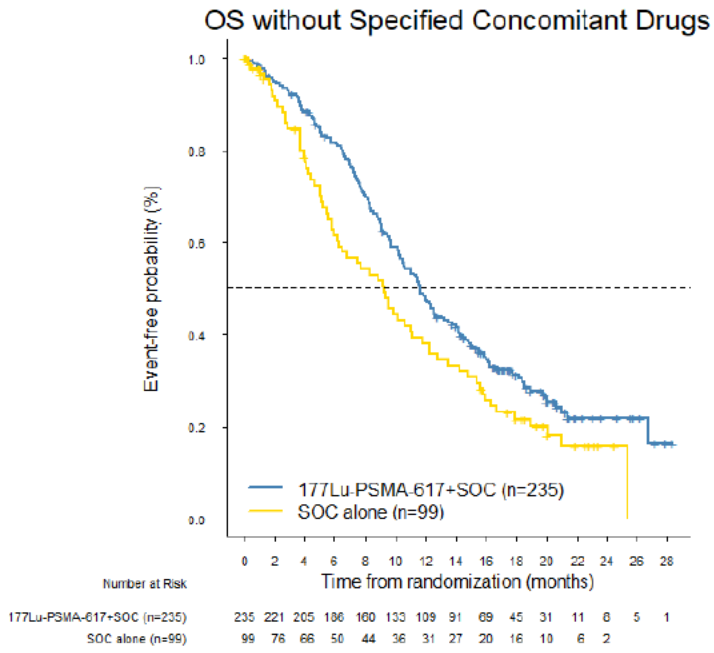
Table 20. Most common concomitant treatments as BSC/BSoC in VISION (FAS safety set)

	177Lu-PSMA-617 +BSC/BSoC N=529 N (%)	BSC/BSoC only N=205 N (%)
Enzalutamide	157 (30)	87 (42)
Abiraterone	134 (24)	72 (26)
Bisphosphanates	45 (9)	28 (14)
Glucocorticoids	335 (63)	134 (65)
GNRH analogues	468 (89)	172 (84)
Radiation therapy	91 (17)	40 (20)

AR inhibitors such as enzalutamide and abiraterone have demonstrated a survival advantage in patients with metastatic hormone sensitive prostate cancer patients and in patients with mCRPC both before and after receipt of docetaxel chemotherapy. However, there is a lack of prospective data to assess their efficacy in a patient population that has received both a taxane chemotherapy and another prior AR inhibitor, such as the population enrolled in VISION.

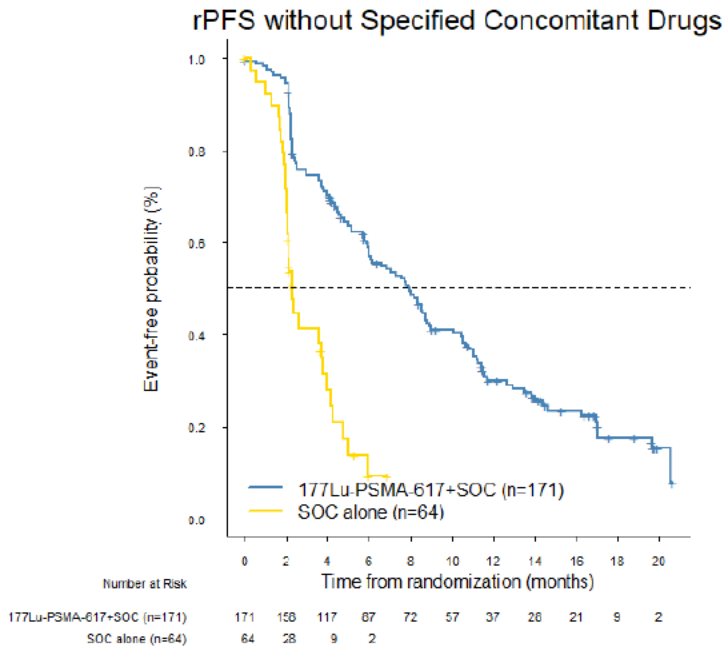
FDA conducted a sensitivity analysis to assess the impact of the receipt of concurrent ARPI on the efficacy outcomes. The results showed that rPFS and OS benefit of adding ^{177}Lu-PSMA-617 to BSC/BSoC was maintained even after excluding patients who received androgen pathway receptor inhibitors.

Figure 4. Sensitivity analysis of the impact of the receipt of concurrent ARPI on the OS and rPFS



	N	Number of deaths	Median OS	95% CI
Pluvicto	235	166	11.6	(10.5, 13.2)
SOC alone	99	68	9.3	(6.3, 12.3)

Excluding patients who received concomitant enzalutamide, abiraterone, apalutamide, bicalutamide, darolutamide, and nilutamide, the OS HR was 0.69 (95% CI: 0.51, 0.92).



	N	Number of rPFS events	Median rPFS	95% CI
Pluvicto	171	121	7.9	(6.1, 9.0)
SOC alone	64	31	2.4	(2.1, 4.0)

Excluding patients who received concomitant enzalutamide, abiraterone, apalutamide, bicalutamide, darolutamide, and nilutamide, the rPFS HR was 0.26 (95% CI: 0.16, 0.41).

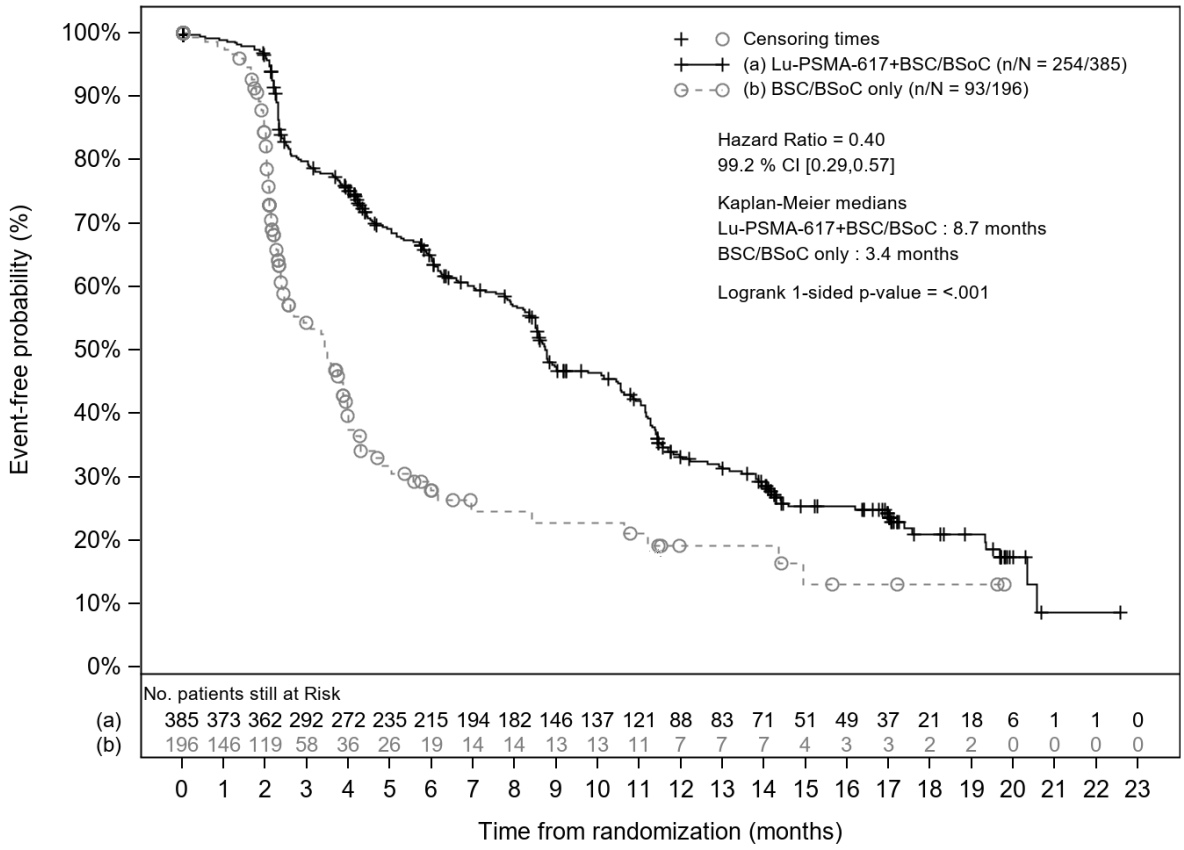
Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

rPFS

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

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

Figure 5: Kaplan-Meier plot of rPFS based on blinded independent central review (PFS-FAS) in Study PSMA-617-01



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

Table 21: rPFS based on a blinded independent central review using stratified log-rank test and Cox regression model (PFS-FAS) in PSMA-617-01

	^{177}Lu-PSMA-617+ BSC/BSoC N=385	**BSC/BSoC only N=196**
rPFS, n (%)		
Events (progression or death)	254 (66.0)	93 (47.4)
Radiographic progressions	171 (44.4)	59 (30.1)
Deaths	83 (21.6)	34 (17.3)
Censored	131 (34.0)	103 (52.6)

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

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

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

[3] Both Cox PH model and Log-rank test are stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no). IRT data for stratification are used.

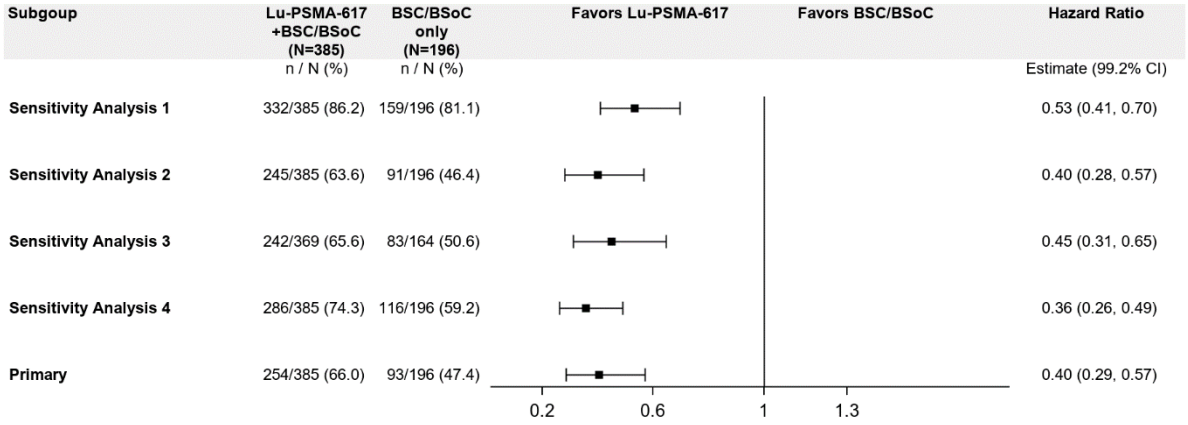
[4] Follow-up time = (Date of event or censoring - randomization date + 1)/30.4375 (months) censoring for death or radiographic progression.

Results of multiple preplanned sensitivity analyses demonstrated that the observed benefit in rPFS was robust, with estimated HRs ranging from 0.36 to 0.53

- Sensitivity analysis 1:
    - Includes events regardless of intervening missed assessments
    - Bone PDs were indicated per PCWG3 guidelines with modified rules for confirmation after week 16
    - Included all radiographic PD and deaths captured in the study, including scans not centrally read that were captured on the LTFU CRF page
- Sensitivity analysis 2: deaths occurring after start of a new anticancer therapy were censored at start date of the new therapy.

- Sensitivity analysis 3: rPFS was defined from the date of first dose of randomized treatment.
- Sensitivity analysis 4: local investigator assessments were used instead of central reading.

Figure 6: rPFS treatment effect sensitivity analyses per blinded independent central review - Forest plot of HR with 99.2% CI (PFS-FAS) in PSMA-617-01



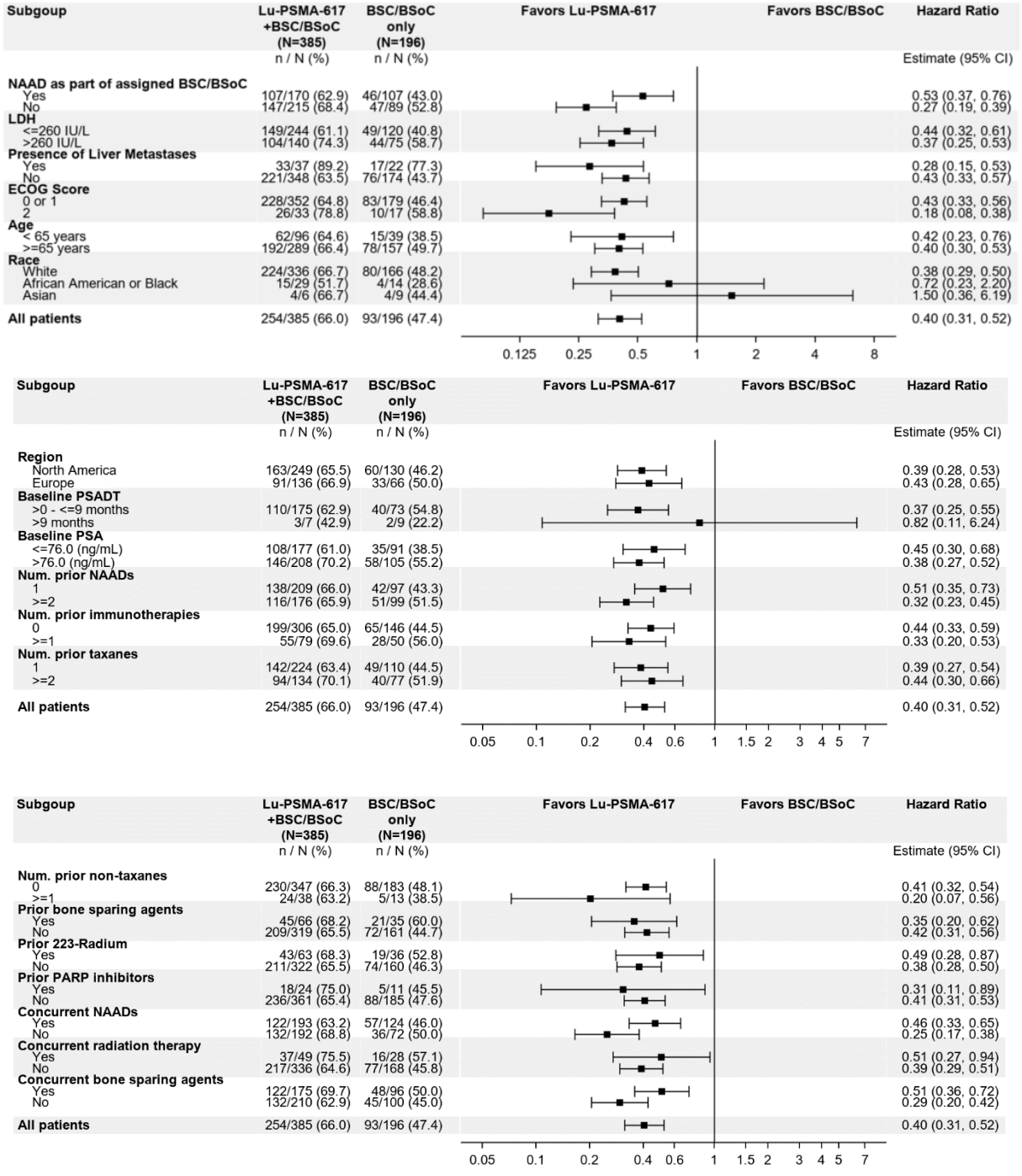
n/N: number of events/number of patients in treatment arm. Vertical line shows the no effect point.

In addition, further analyses on rPFS were performed:

- The robustness of the primary analysis was further confirmed by an analysis of rPFS conducted based on the FAS.
- Sensitivity analyses assessed the impact of COVID-19 on rPFS. Results were also similar to those for the primary analysis.
- A panel of analyses were also performed to assess the sensitivity of rPFS to censoring due to drop-outs. These were also consistent with the primary analysis of rPFS.

Subgroup analyses of rPFS were consistent with the primary rPFS analysis and demonstrated homogeneity of the treatment effect across these subgroups, with the exception of subgroups with too few patients to be interpretable (e.g. Asian, African American or Black, and PSA doubling time (PSADT) >9 months subgroups). See Figure .

Figure 7: rPFS treatment effect for patient subgroups per blinded independent central review - Forest plot of HR with 95% CI (PFS-FAS) in Study PSMA-617-01

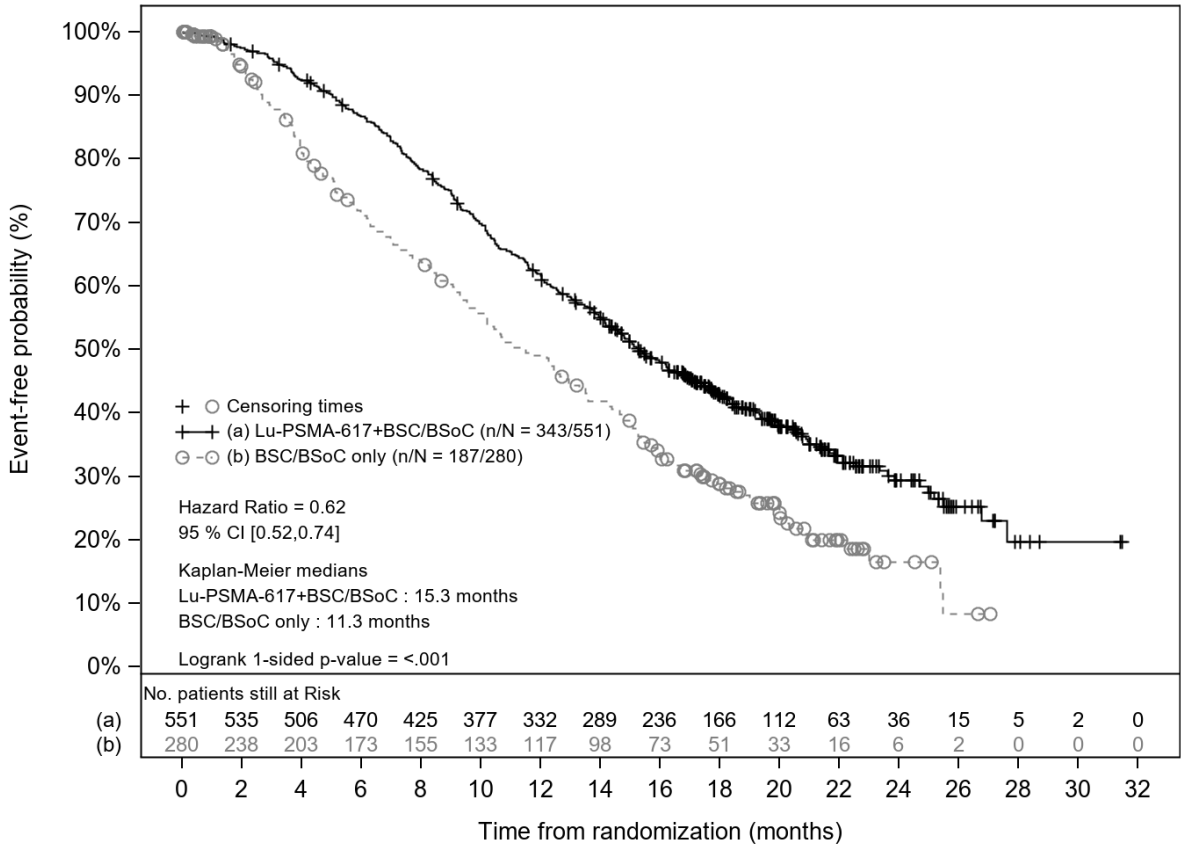


n/N: number of events/number of patients in treatment arm.Vertical line shows no effect point.

Overall survival

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

Figure 8: Kaplan-Meier plot of OS (FAS) from PSMA-617-01



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

The HR was 0.62 (95% CI: 0.52, 0.74) in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm vs. BSC/BSoC only, with a median OS of 15.3 months (95% CI: 14.2, 16.9) and 11.3 months (95% CI: 9.8, 13.5), respectively (Table 22). Thus, the median OS was prolonged by 4.0 months.

Table 22: OS using stratified log-rank test and Cox regression model (FAS) in PSMA-617-01

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

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

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

- An OS analysis based on the PFS-FAS was consistent with the primary analysis
- A sensitivity analysis of OS to assess the impact of COVID-19 was also consistent with the primary analysis.

- An analysis of OS was conducted based on the first 750 patients randomized, and was also consistent with the primary analysis
- A panel of analyses were performed to assess the sensitivity of OS to censoring due to drop-outs. These were also consistent with the primary analysis of OS

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

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

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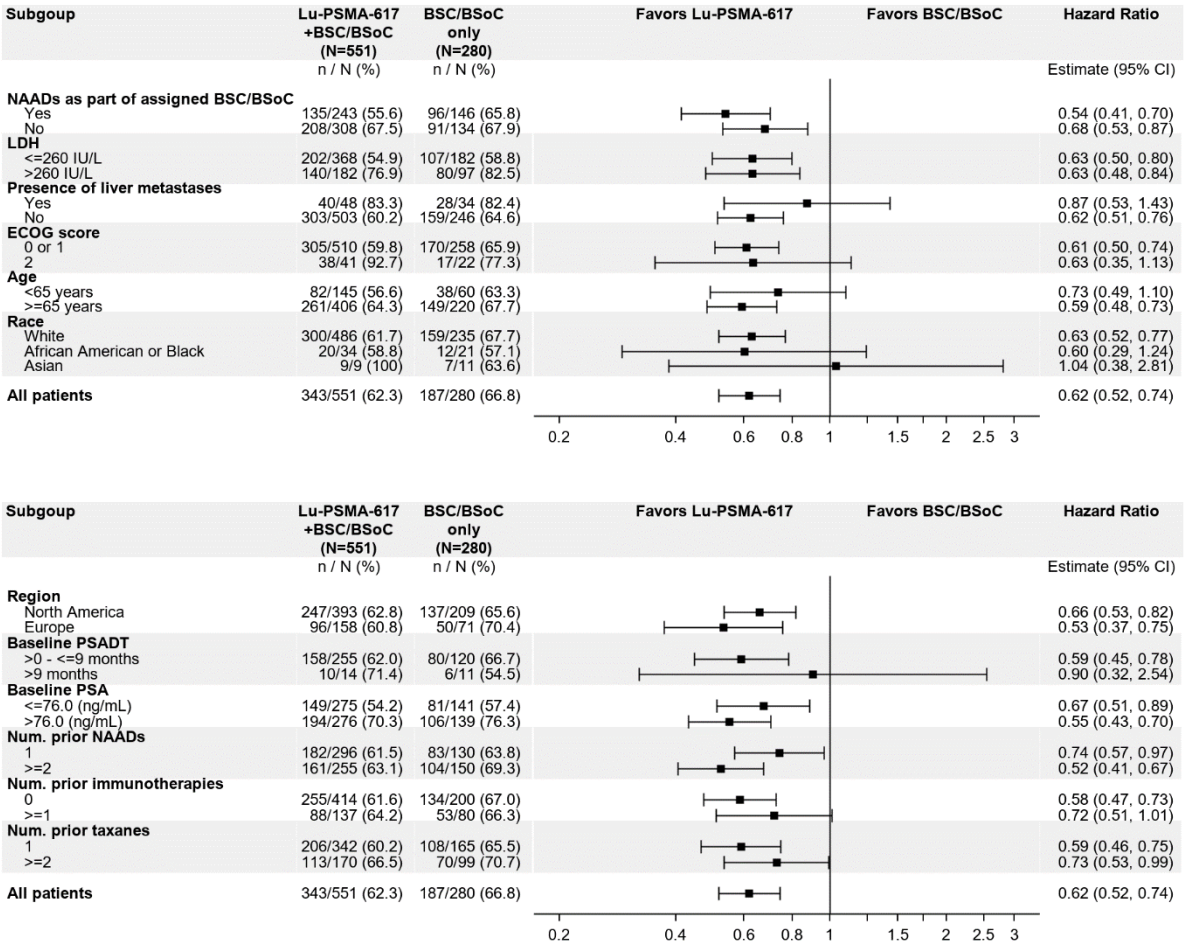
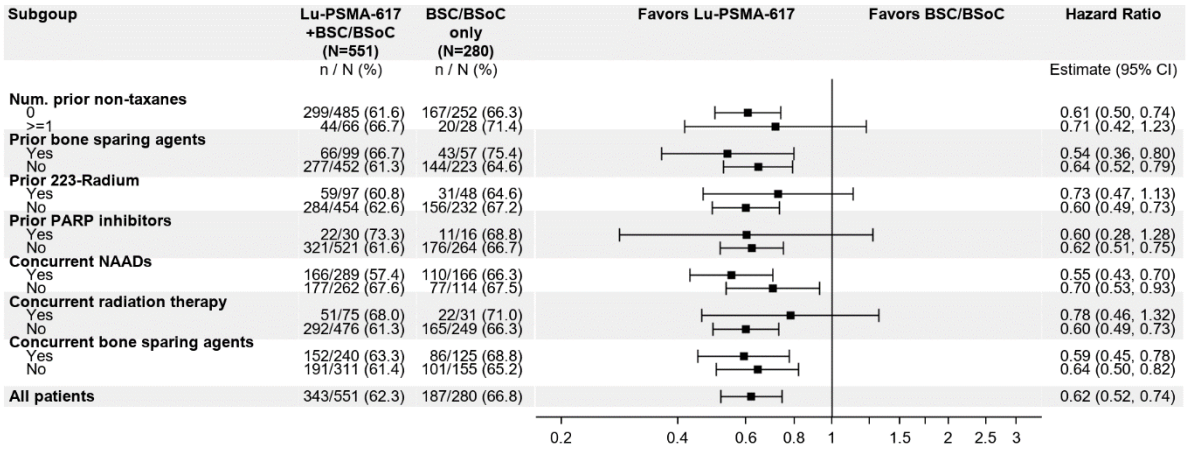
Figure 9: OS subgroup analysis: forest plot of HR with 95% CI (FAS) in PSMA-617-01





n/N: Number of events/number of patients in treatment arm. Vertical line shows no effect point.

The Applicant's Position:

The study met both alternate primary efficacy objectives.

Note, there was a low representation of patients who were Black or African American (6.6% of patients overall) or Asian (2.4%). However, this was balanced between the two treatment arms. Demographic and baseline disease characteristics (including prognostic factors) were well balanced between the two treatment arms, providing reassurance as to the interpretation of treatment comparisons. The COVID-19 pandemic had minimal impact on the conduct of this study, and sensitivity analyses showed that the pandemic had no impact on the alternate primary efficacy endpoints evaluations.

The FDA's Assessment:

FDA agrees with the primary analysis results and sensitivity analysis results for OS and rPFS presented by the Applicant. The OS HR was 0.62 (95% CI: 0.52, 0.74) based on the FAS (N=831), which included all randomized patients (the intent to treat [ITT] analysis set).

The rPFS HR was 0.40 (95% CI: 0.31, 0.52) based on the PFS-FAS (N=581), which included all patients randomized on or after March 5, 2019.

The HRs were consistent across exploratory subgroups, including age, region, and other stratification factors. FDA evaluated several important review issues in detail as articulated below.

Withdrawal of consent

The primary review issue surrounded the fact that the VISION trial had considerable withdrawal of consent and disproportionate dropout in the BSoC only (control) arm. This was felt to be

attributed to the non-blinded trial design, with patients withdrawing consent in the control arm when they realized they were not going to receive the investigational therapy. The Applicant implemented corrective actions during the trial and withdrawal of consent decreased considerably as a result. As noted earlier in this review, rPFS was prospectively analyzed in the analysis population of patients randomized *after* these measures were implemented (PFS-FAS analysis set). This PFS-FAS analysis set served to mitigate, but did not eliminate, the extent of withdrawal which could bias the analysis of rPFS in particular, because rPFS data could not be collected for the patients with early dropout. Table 21 notes approximately 20% more censoring of rPFS in the control arm compared to the investigational arm and adequate tumor assessments were not available for 18% of the control arm patients compared with only 1.3% on the PLUVICTO arm. While sensitivity analyses support the robust statistical difference in rPFS favoring PLUVICTO, asymmetric censoring creates uncertainty around the true magnitude of delay in tumor progression which is problematic for an endpoint that relies heavily on the magnitude of effect to support clinical meaningfulness.

OS was analyzed in all randomized patients (FAS analysis set). This is because in addition to improvement in dropout with the corrective measures, the effect of early withdrawal on survival was further mitigated by the ability to ascertain survival status where feasible. Patients could still be followed for overall survival via public registries if they dropped out, and this was specified in the site specific informed consent. Thus, a substantial number of patients who withdrew consent early still had available OS data used in the primary analysis (OS FAS analysis set) which mitigated, although did not completely eliminate, asymmetric censoring for OS. FDA further investigated the concern that asymmetric censoring due to withdrawal of consent could impact efficacy results. In the FAS for OS, 15 patients (2.7%) were censored due to withdrawal of consent in the ^{177}Lu-PSMA-617 arm compared to 33 patients (11.8%) in the BSoC arm. Among this subset of patients, the observed median time from randomization to date of censoring due to withdrawal of consent was 8.4 (range: 1 - 18.6) months in the ^{177}Lu-PSMA-617 arm and 0.7 (range: 0.03 - 8.1) months in the BSoC arm.

Several sensitivity analyses were conducted by the Applicant to assess the impact of censoring due to drop-outs for both OS and rPFS results in the FAS and PFS-FAS populations, respectively.

Table 23: Sensitivity Analyses of OS and rPFS Assessing Impact of Censoring Due to Drop-Outs

OS (FAS)	Scenario	HR (95% CI)
Analysis per protocol	Censored as it is	0.62 (0.52, 0.74)
Extreme case	The seleted extreme case scenario	0.66 (0.55, 0.79)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.8 (0.67, 0.96)

Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.76 (0.64, 0.91)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.63 (0.53, 0.76)
Multiple imputation under informative censoring	Hazard decrease by 38% in BSC/BSoC arm after censoring*	0.68 (0.56, 0.82)
Tipping point 1: largest upper 95% CI	Hazard decrease by 99% in BSC/BSoC arm after censoring*	0.84 (0.7, 1.00)
Tipping point 2: extreme case	Hazard decrease by 27% in BSC/BSoC arm after censoring*	0.66 (0.55, 0.79)
rPFS (PFS-FAS)	**Scenario**	**HR (99.2% CI)**
Analysis per protocol	Censored as it is	0.4 (0.29, 0.57)
Extreme case	The seleted extreme case scenario	0.42 (0.3, 0.6)
Multiple imputation under best patients	Hazard in BSC/BSoC arm based on best 20% patients across both arms	0.77 (0.55, 1.07)
Multiple imputation under best BSC/BSoC patients	Hazard in BSC/BSoC arm based on best 20% BSC/BSoC patients	0.56 (0.4, 0.79)
Multiple imputation under non-informative censoring	Hazard remains unchanged after censoring	0.4 (0.29, 0.56)
Multiple imputation under informative censoring	Hazard decrease by 60% in BSC/BSoC arm after censoring*	0.54 (0.38, 0.77)
Tipping point 1: largest upper 99.2% CI	Hazard decrease by 85% in BSC/BSoC arm after censoring*	0.71 (0.5, 1.01)
Tipping point 2: extreme case	Hazard decrease by 11% in BSC/BSoC arm after censoring*	0.42 (0.3, 0.59)

Source: Applicant-provided Summary of Clinical Efficacy, Appendix 1, Tables 29-30
*Risk of event remains unchanged after censoring in the investigational arm

The Applicant's sensitivity analyses increased and decreased survival chance for OS and rPFS for both treatment arms by varying levels. For example, the extreme case analysis considered all

drop-outs in the the ^{177}Lu-PSMA-617 arm as events, which assumes a shortened survival time on ^{177}Lu-PSMA-617 arm. The two best case analyses assumes elongated survival in the BSoC arm by imputing data for drop-outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSoC only arm. The tipping-point analysis quantified the increase or decrease in the risk of event in patients dropping out of the ^{177}Lu-PSMA-617 arm or the BSoC arm that would make the primary analysis lose statistical significance. For example, in tipping point analysis 1 for OS, the hazard of survival would need to decrease by 99% on the BSoC arm in order for OS to become non-statistically significant, which is considered extreme and very unlikely to occur.

The review team conducted an additional OS sensitivity analysis by excluding patients who withdrew consent. The HR was 0.62 (95% CI: 0.52, 0.75), which was also consistent with the primary analysis of OS.

FDA's statistical review of this issue concluded that while the disproportionate drop out in the BSoC arm compared to the ^{177}Lu-PSMA-617 was concerning, ascertainment of many of the OS events from withdrawn patients as well as multiple sensitivity analyses that considered extreme cases and the possibility of informative censoring continued to support the statistical significant primary analysis results for both OS and rPFS.

Sensitivity analyses support a robust statistically significant effect on Overall Survival, and the degree of asymmetric censoring was less for OS than for rPFS. Nonetheless, sensitivity analyses suggest there could still be some diminution of the OS magnitude of effect. The review team felt that the precision of OS as an endpoint and its meaningfulness as a clinical outcome are such that even a slightly smaller magnitude in the delay in death than what is reported would still be meaningful and support a favorable benefit:risk for this patient population. The rPFS analysis was limited by a larger degree of censoring and smaller analysis population. Because of the higher uncertainty surrounding the meaningfulness of the magnitude of the rPFS difference, the numeric results for rPFS will not be included in FDA product labeling.

Efficacy results from key secondary endpoints including durable ORR were consistent and supported the observed efficacy of ^{177}Lu-PSMA-617.

Number of 177Lu-PSMA-617 cycles received

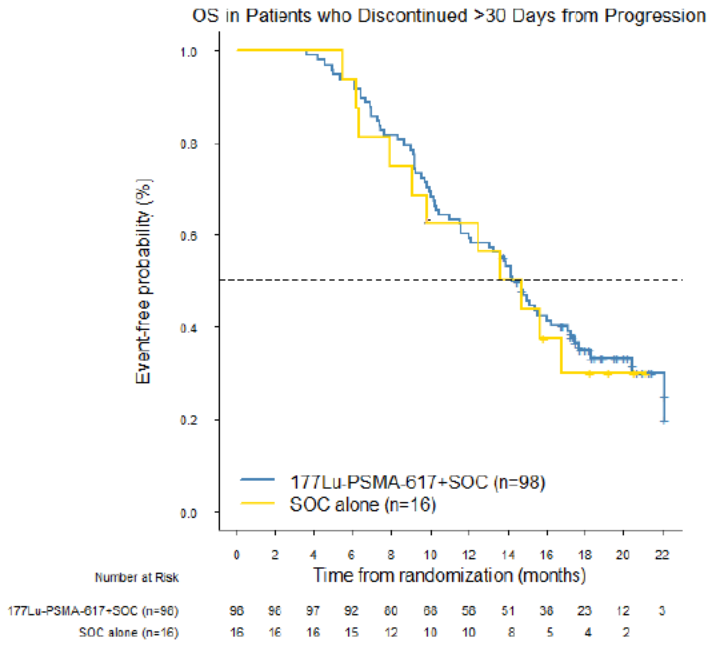
To further evaluate the robustness of the observed benefit of rPFS and OS based on drug exposure, FDA conducted additional sensitivity analyses on these endpoints by number of cycles of ^{177}Lu-PSMA-617+BSC/BSoC received. The rPFS HR was 0.15 (95% CI: 0.11, 0.21) and the OS HR was 0.18 (95% CI: 0.14, 0.24), where the HR is comparing 5-6 cycles to ≤4 cycles of ^{177}Lu-PSMA-617+BSC/BSoC received. These subgroup results should be interpreted with caution because the sample size in each subgroup was not planned to power such analyses.

Therefore, the subgroup analyses are considered exploratory. Additionally, there is inherent bias in comparing outcomes by number of cycles received, as only patients who were responding to treatment continued to receive additional cycles of the investigational therapy. This further confounds interpretation of this sensitivity analysis and the results should be interpreted with caution.

Patients who discontinued study treatment > 30 days from earliest radiographic progression

The proportion of patients with radiographic disease progression that discontinued study treatment > 30 days from their earliest radiographic progression was higher in the investigational arm. A sensitivity analysis was conducted to assess the potential effect of this imbalance on rPFS and OS.

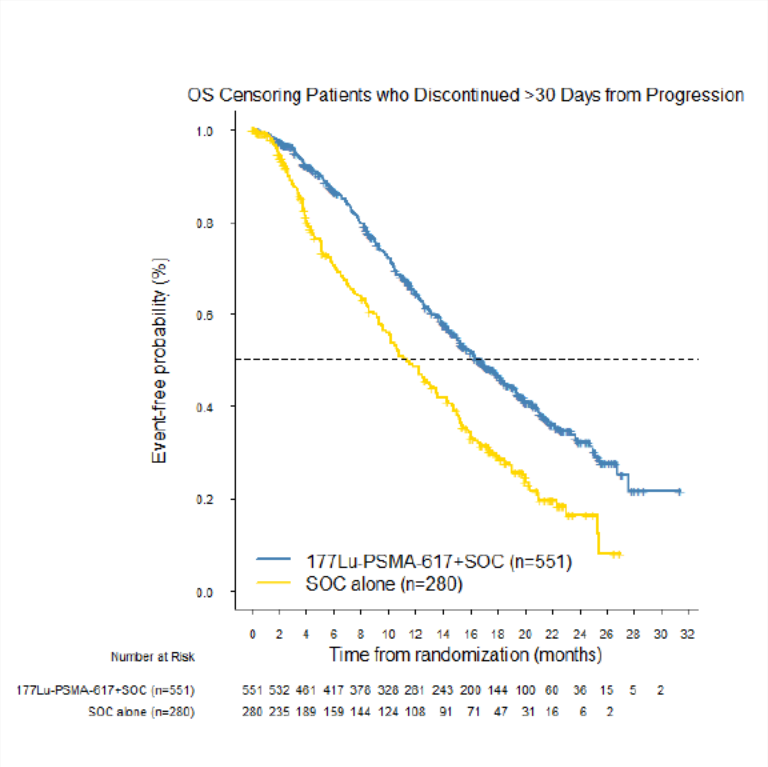
Figure 10. Sensitivity Analyses in Patients who Discontinued >30 Days from Progression Subset of Patients who Discontinued >30 Days from Progression



	N	Deaths	Median (months)	95% CI
^{177}Lu-PSMA-617 + BSoC/BSC	98	65	14.2	(12.1, 17.2)
BSoC/BSC	16	11	14.1	(9.07, NR)

Hazard Ratio: 0.72 (95% CI: 0.36, 1.43)

All Patients Censoring Patients Who Discontinued >30 Days from Progression at Time of Progression



	N	Deaths	Median (months)	95% CI
^{177}Lu-PSMA-617 + BSoC/BSC	551	278	16.8	(15.1, 18.5)
BSoC/BSC	280	176	11.3	(9.8, 13.5)

Hazard Ratio: 0.57 (95% CI: 0.47, 0.70)

The HRs for rPFS and OS continued to be in favor of ^{177}Lu-PSMA-617 even when accounting for patients who may have gotten more BSoC treatment beyond radiographic progression.

Despite a higher proportion of concurrent newer anti-androgen drugs (NAAD, otherwise known as newer hormonal agents [e.g. abiraterone, enzalutamide]), bone targeting agents, and/or radiation therapy in BSC/BSoC arm, there was improved rPFS and OS in ^{177}Lu-PSMA-617+BSC/BSoC arm. These findings further support the efficacy demonstrated by the primary efficacy outcome measures.

PSMA

On October 27th, 2021, the Applicant submitted data on tumor characteristics on ^{68}Ga-PSMA-11 PET CT scan. To further assess whether a flat dose is appropriate for all the patients, the FDA requested that the Applicant performs additional analysis of these data to explore the relationship between safety and efficacy outcomes with baseline body weight and disease burden in patients who received ^{177}Lu-PSMA-617 in VISION. Disease burden was defined as the volume of segmented PSMA positive tumor (PSMA + tumor volume) in the whole body using ^{68}Ga-PSMA-11 PET imaging. Disease burden was categorized as <median value of PSMA + tumor volume in the whole body vs ≥median value. The median PSMA + tumor volume in the whole body was derived using all patients randomized to the ^{177}Lu-PSMA-617 + BSoC/BSC arm who had good quality images available. The analysis of rPFS and OS by baseline body weight and PSMA-positive tumor volume in the whole body are presented in the table below.

Table 24. Summary of rPFS per BICR (PFS-FAS) and OS (FAS) by baseline body weight and PSMA-positive tumor volume (cc) in whole body, in the ^{177}Lu-PSMA-617 + BSoC/BSC arm

Body weight (BW) and tumor volume (TV) in whole body	Median rPFS (95%CI) in months	Median OS (95%CI) in months
BW <80 and TV < 398.144 cc	11.0 (8.3 to 17.0)	17.9 (14.8 to 20.5)
BW <80 and TV ≥ 398.144 cc	8.5 (5.2 to 10.5)	11.6 (10.5 to 13.9)
BW ≥80 and TV < 398.144 cc	11.3 (8.5 to 14.2)	24.7 (20.8 to 26.8)
BW ≥80 and TV ≥ 398.144 cc	8.0 (6.1 to 8.7)	11.6 (10.2 to 13.8)

The results of the analysis demonstrated that patients with lower PSMA-positive tumor volume at baseline had better rPFS and OS compared to patients with high tumor volume, regardless of the body weight. Patients with metastatic cancer with a lower tumor burden may inherently have less biologically aggressive disease, which may explain their better outcomes. However, this analysis is only considered exploratory and no definitive conclusions can be drawn from the results of this analysis.

In VISION, patients were excluded if any lesions exceeding size criteria in short axis [organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm] had uptake less than or equal to uptake in normal liver. Data on activity of ^{177}Lu-PSMA-617 in patients with negative-PSMA lesions is limited at this time.

A retrospective study of 54 patients with mCRPC treated with ^{177}Lu-PSMA 617 showed that median OS was better in patients who did not have any PSMA-negative lesion (Michalski, et al. 2021): Median OS 6 months in patients (n=18) with ≥1 PSMA-negative lesion; Median OS 16 months in patients (n=36) with all PSMA-positive lesions. Data from the published literature have shown antitumor activity (≥50% PSA decline response) of PSMA-targeted radionuclide therapies even in mCRPC with low or negative PSMA expression on PSMA-PET (Vlachostergios, et al. 2021). Additionally, in VISION, one patient with negative scan received ^{177}Lu-PSMA 617.

The patient initially met the selection criteria for PSMA expression, however, a second PSMA PET which was performed within 28 days of treatment initiation did not meet the criteria and patient was excluded from the analysis. However, the patient received 6 doses of 177Lu-PSMA 617, achieved a complete response and was still alive at the time of submission of this NDA. At this time, the efficacy of ^{177}Lu-PSMA 617 in patients who did not meet eligibility for VISION is unknown.

Data Quality and Integrity

The Applicant's Position:
No data integrity concerns were reported following completion of site inspections by the Sponsor.

The FDA's Assessment:
There were no concerns regarding data quality or integrity identified during review of this application.

Efficacy Results – Secondary and other relevant endpoints

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

All key secondary endpoints showed a statistically significant benefit: ORR (29.8% with a durable response, median DoR of 9.8 months), DCR (89.0%), and time to first SSE (an estimated 50% reduction in the risk of a SSE or death when compared with BSC/BSoC only) (Table 25, Figure).

Table 25: Key secondary efficacy results in PSMA-617-01

	^{177}Lu-PSMA-617+BSC/BSoC	BSC/BSoC only
Response evaluable analysis set	**N=319**	**N=120**
Overall Response Rate (ORR: CR+PR), n (%)	95 (29.8)	2 (1.7)
Odds Ratio [95% CI][1]	24.99 [6.05, 103.24]	
Two-sided p-value[1]	< 0.001	
Disease Control Rate (DCR CR+PR+SD+Non-CR/ Non-PD > 6 weeks), n (%)	284 (89.0)	80 (66.7)
Odds Ratio [95% CI][1]	5.79 [3.18, 10.55]	
Two-sided p-value[1]	< 0.001	
Duration of Response (DoR) (months), n (%)[2]		
KM Median DoR [95% CI]	9.8 [9.1, 11.7]	10.6 [NE, NE]

	^{177}Lu-PSMA-617+BSC/BSoC	BSC/BSoC only
PFS-FAS set	**N=385**	**N=196**
Time to first symptomatic skeletal event (SSE), n (%)		
KM Median time to SSE [95% CI]	11.5 [10.3, 13.2]	6.8 [5.2, 8.5]
Hazard Ratio (Stratified Cox PH model)[3, 4]	0.50	
95% CI	[0.40, 0.62]	

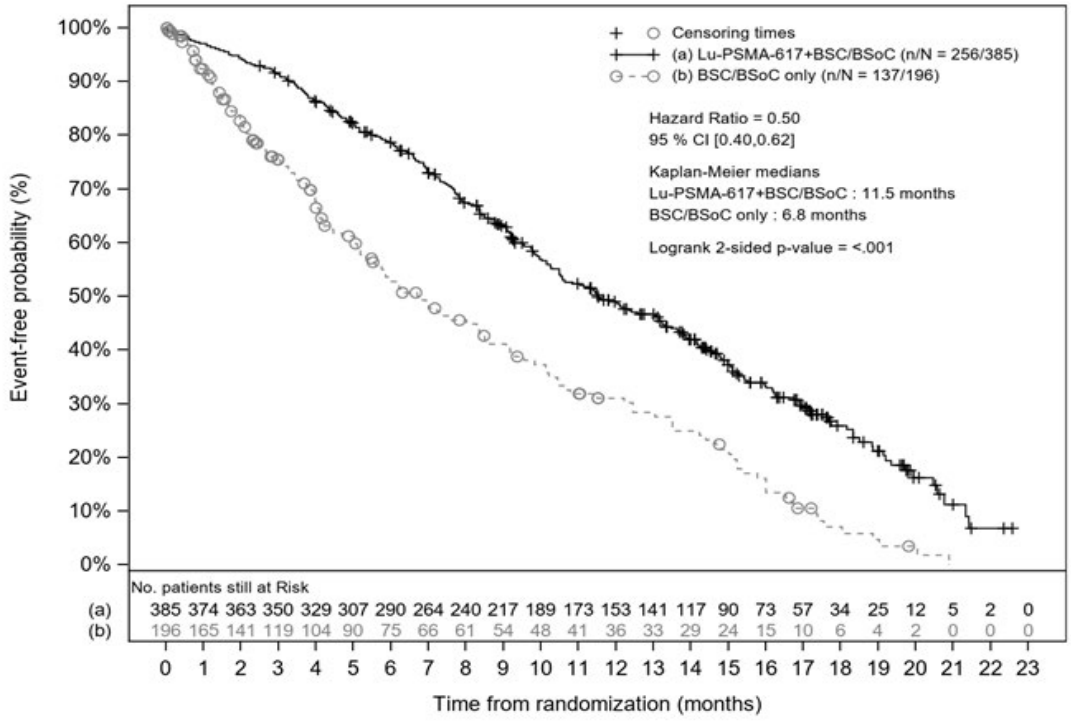
[1] Odds Ratio of ^{177}Lu-PSMA-617+BSC/BSoC vs. BSC/BSoC only based on logistic regression model stratifying for the randomization stratification factors, LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no). IRT data for stratification are used. P-value based on Wald's Chi-Square test.

[2] DoR is not a key secondary endpoint

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

[4] Cox PH model is stratified for LDH (≤ 260 IU/L vs. > 260 IU/L); presence of liver metastases (yes vs. no); ECOG score (0 or 1 vs. 2); and inclusion of NAAD in BSC/BSoC at time of randomization (yes vs. no). IRT data for stratification are used patients (months); SE: standard error; EDoR: expected duration of response (months) equals Mean DoR X Overall Response Rate.

Figure 11: Kaplan-Meier plot of time to first SSE (PFS-FAS) from PSMA-617-01



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

Since many other therapies have failed by this stage of disease management, the ability to control disease progression in this heavily pretreated population is of clinical importance. The longer time to occurrence of a SSE is also beneficial, since it enables continued ambulation and freedom of movement in these patients. These improvements are accompanied by improvements in PFS, biochemical response, and PROs, as discussed in the "**Efficacy Results – Secondary or exploratory Clinical Outcome Assessment (COA)/Patient Reported Outcome (PRO) endpoints**" section below.

The Applicant's Position:
The study also met all of its key secondary efficacy objectives.
Other secondary efficacy analyses, including progression-free survival, biochemical response and PRO (including prostate specific FACT-P and pain specific BPI analyses), although not adjusted for statistical significance, were in favor of the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The FDA's Assessment:
FDA agrees with the secondary analysis results for ORR, DCR, and time to SSE presented by the Applicant.

Disease control rate (DCR) includes patients with stable disease. DCR is difficult to interpret because stable disease may be related to the underlying characteristics of a patient's tumor rather than being reflective of the efficacy of the investigational therapy. ORR is a better measure of investigational drug activity, as this only includes patients who achieve a response (e.g. CR or PR). In patients with mCRPC, tumors are unlikely to spontaneously regress without intervention. Thus, responses as measured by ORR can be attributed to activity of the investigational drug.

The response rate of approximately 30% with median of 10 months compares favorably with alternative systemic treatments that could be available in this population such as repeat taxane treatment. Of note, this overall response rate includes 18 patients (5.6%) who achieved complete response (CR).

Due to the very small number of responses in the control arm, the DOR estimate in this arm is not reliable and can be misleading.

Time to first SSE was defined as the time (in months) from the date of randomization to first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death due to any cause, whichever occurred first. In VISION, most of the events that defined an SSE were death events. Out of 256 events (66.5%) in the ^{177}Lu-PSMA-617 arm and 127 events

(70%) in the BSC arm, only 60 events (15.6%) and 34 events (17.3%), respectively, were non-death events. While supportive of the benefit of 177-LuPSMA-617, the difference in HR for SSE is mainly driven by the difference in OS between the arms rather than by the other events outlined in the definition of an SSE. In addition, sensitivity analyses to take into account asymmetric censoring were not applied to the SSE endpoint. (b) (4)

(b) (4)

Dose/Dose Response

The Applicant's Position:

No exposure-efficacy analysis were conducted.

The FDA's Assessment:
FDA has no additional comment.

Durability of Response

The Applicant's Position:
The DOR is presented in Section 8.1.2: Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
Due to the very small number of responses in the control arm (2 responses [2%]), the DOR estimate in this arm is not reliable and can be misleading. DOR will not be included in labeling.

Persistence of Effect

The Applicant's Position:
In Study PSMA-617-01, a statistically significant improvement in rPFS was demonstrated for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided), with an estimated 60% risk reduction of radiographic disease progression or death (HR=0.40; 99.2% CI: 0.29, 0.57). The median follow-up time for rPFS in the PFS-FAS differed between the 2 treatment arms (16.4 months in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 3.9 months in the BSC/BSoC arm). Radiographic progression-free probability remained higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy.

Likewise, a statistically significant improvement in OS was demonstrated in Study PSMA-617-01 for patients receiving ^{177}Lu-PSMA-617+BSC/BSoC compared to patients receiving BSC/BSoC only (stratified log-rank test $p < 0.001$, one-sided). There was an estimated 38% risk reduction of death in ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm (HR=0.62; 95% CI: 0.52, 0.74). The median follow-up times for OS were similar between the 2 treatment arms (20.3 months [95% CI: 19.8, 21.0] vs. 19.8 months [95% CI: 18.3, 20.8] in the ^{177}Lu-PSMA-617+BSC/BSoC and BSC/BSoC only arms, respectively). The Kaplan-Meier curves for OS diverged after approximately 2 months, remaining higher during the entire follow-up period for the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm, indicating an early and sustained advantage for ^{177}Lu-PSMA-617 therapy.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Efficacy Results – Secondary or exploratory Clinical Outcome Assessment (COA)/Patient Reported Outcome (PRO) endpoints

The Applicant's Position:

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

FACT-P total score showed an estimated 46% risk reduction in worsening from baseline, clinical progression or death in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with the BSC/BSoC only arm across its many subscales and components. There was a delayed time to worsening of the FACT-P total score with a median time of 5.7 months (95% CI: 4.8, 6.6) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared with 2.2 months (95% CI: 1.8, 2.8) in the BSC/BSoC only arm.

BPI-SF showed that patients were more stable with less pain and lower interference with daily activities in the ^{177}Lu-PSMA-617+BSC/BSoC arm, with the BSC/BSoC only arm experiencing a greater degree of variation:

- For the BPI-SF pain intensity scale: there was an estimated 48% reduction in risk of worsening, clinical progression or death (HR = 0.52; 95% CI: 0.43, 0.63; Cox two-sided p-value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm
- For the BPI-SF pain interference scale: there was an estimated 43% reduction in risk of worsening, clinical progression or death (HR = 0.57; 95% CI: 0.47, 0.69; Cox two-sided p-

value: < 0.001) in the ^{177}Lu-PSMA-617+BSC/BSoC arm compared to the BSC/BSoC only arm

The FDA's Assessment:
Because there is no pre-specified statistical testing procedure to control for Type I error, all PRO analyses are considered to be exploratory only.

The quality of the PRO data, degree of censoring and use of PRO time to event analyses significantly limited the ability for FDA use this information to inform risks or benefits of the effect of 177-Lu-PSMA-617.

This information is not included in labeling.

Additional Analyses Conducted on the Individual Trial
The Applicant's Position:
rPFS, OS, PFS and PROs (FACT-P total score, FACT-G total score, BPI-SF pain interference, and BPI-SF pain intensity) were also analyzed in the ^{177}Lu-PSMA-617 + BSC/BSoC arm of the FAS safety analysis set by number of ^{177}Lu-PSMA-617 cycles. The sub-group analyses results from Study PSMA-617-01 in the 69 patients who received 4 cycles, and the 289 patients who received 5-6 cycles (FAS Safety set) also provide additional evidence for using a total of 6 cycles:

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

- Median **time to worsening in BPI-SF pain interference** for patients who received 4 cycles of ^{177}Lu-PSMA-617 was 5.6 months (95% CI: 4.4, 6.0); for patients who received 5-6 cycles, median time to worsening in BPI-SF pain interference was 8.8 months (95% CI: 7.4, 10.4).

All other relevant details have been discussed in the sections above.

The FDA's Assessment:
Due to the small sample sizes of the subgroups analyzed, these rPFS, OS, and PFS analyses should be interpreted with caution. PRO data and analytic methods were not felt to be interpretable as mentioned above.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
This section is not applicable, as there was only one pivotal trial. See Section 8.1.5, "Integrated Assessment of Effectiveness" for assessment of effectiveness in the pivotal VISION trial.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:
Not Applicable

The FDA's Assessment:
FDA agrees with the Applicant's position.

Secondary and Other Endpoints

The Applicant's Position:
Not Applicable

The FDA's Assessment:
FDA agrees with the Applicant's position.

Subpopulations

The Applicant's Position:
Not Applicable

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Efficacy Considerations

The Applicant's Position:
Not Applicable

The FDA's Assessment:
FDA agrees with the Applicant's Position. This section is not applicable, as there was only one pivotal trial to support this application.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:
The results of Study PSMA-617-01 demonstrated that treatment with ^{177}Lu-PSMA-617 consistently resulted in statistically significant and clinically meaningful improvements in key measures of efficacy, including reduced risk of radiographic disease progression or death, a reduced risk of death, increased ORR and DCR, and delay in time to first SSE.
Study PSMA-617-01 met its primary objectives for both alternate primary endpoints. Statistically significant improvements were demonstrated in favor of treatment with ^{177}Lu-PSMA-617+BSC/BSoC relative to BSC/BSoC only.

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

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

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

- An HR ≤ 0.8 corresponding to an improvement in median OS within the range of 2.5 to 6 months
- Incremental gains in other efficacy and key secondary endpoints

Homogeneity and consistency of the alternate primary endpoints rPFS and OS were evident across subgroups, including stratification factors, age, region, baseline PSA, prior therapies, and concurrent therapies, demonstrating a consistent beneficial treatment effect. The only exception was subgroups with too few patients to be interpretable.

The FDA's Assessment:

The efficacy of ^{177}Lu-PSMA-617 in patients with histologically or cytologically confirmed mCRPC that has previously been treated with at least one AR inhibitor and one or two taxane regimens and who had PSMA-positive ^{68}Ga–labeled PSMA-11 PET-CT scans is supported by one randomized, open-label, multi-national, controlled phase 3 clinical study, VISION.

The alternative primary endpoints were rPFS (per PCWG3) and OS. Either could be positive to satisfy primary endpoint. The primary endpoint of OS was met, with patients randomized to receive ^{177}Lu-PSMA-617 having prolonged OS (median estimate 15.3 months) compared to BSC/BSoC (median estimate 11.3 months), HR 0.62 (95% CI: 0.52, 0.74, p<0.001). The primary endpoint of BICR assessed rPFS was also met, with patients randomized to receive ^{177}Lu-PSMA-617 plus BSC/BSoC having prolonged rPFS (median estimate 8.7 months) compared to BSC/BSoC (median estimate 3.4 months), HR 0.40 (95% CI: 0.31, 0.52, p<0.001). Secondary endpoints (e.g. ORR by RECIST and delay in time to first SSE) also favored ^{177}Lu-PSMA-617.

Disproportionate drop out due to withdrawal of consent in the control arm was a key review issue. The potential effect of drop out on the primary efficacy endpoints was mitigated by obtaining survival status in the subset of patients who withdrew where feasible. The FDA focused its conclusion of efficacy on the OS endpoint. In the OS FAS analysis, 15 patients (2.7%) were censored due to withdrawal of consent in the ^{177}Lu-PSMA-617 arm compared to 22 patients (11.8%) in the BSoC arm. The primary OS finding was statistically persuasive with robust magnitude of effect. Multiple sensitivity analyses conducted by the Applicant demonstrated that the OS benefit was maintained when assessing the impact of censoring due to drop-outs. An extreme case analysis considered all drop-outs in the the ^{177}Lu-PSMA-617 arm as events. Two best case analyses imputed data for drop-outs in the control arm based on the HR in the 20% of patients with the longest survival either overall or in the BSoC only arm. A

tipping-point analysis quantified the increase or decrease in the risk of event in patients dropping out of the ^{177}Lu-PSMA-617 arm or the BSoC arm that would make the primary analysis lose statistical significance. The results of these sensitivity analyses were reviewed by the FDA statistical team and felt to be supportive of a statistically significant and meaningful effect on survival despite the limitation of asymmetric censoring. OS results were supported by the rPFS results which were also subject to sensitivity analyses as well as a durable objective response rate of 30% with a portion of patients achieving complete response.

The FDA agrees that the observed OS benefit of adding ^{177}Lu-PSMA-617 to BSC/BSoC is statistically significant and clinically meaningful. Results of sensitivity analyses and subgroup analyses of BICR-rPFS and OS supported the primary findings. Patients with mCRPC who have received a prior AR therapy and taxane chemotherapy represent an incurable population with a high unmet medical need. The systemic effect of ^{177}Lu-PSMA-617 may also represent an advance that is clinically meaningful to patients, as the only other radioisotope-based therapy, radium-223, is bone-directed and only indicated in patients with symptomatic bone metastases and no visceral metastatic disease. ^{177}Lu-PSMA-617 demonstrated that it can treat prostate cancer that has metastasized not only in the bone, but also in other areas (e.g. soft tissue) affected by the disease, as evidenced by an objective response rate (per RECIST) of 30%.

Given the OS benefit supported by key subgroup and sensitivity analyses, with consistency across secondary endpoints and a favorable safety profile, the FDA review team concludes that the submitted evidence meets the statutory evidentiary standard for regular approval of ^{177}Lu-PSMA-617 for the proposed indication.

(b) (4)

(b) (4) PSMA expression is associated with more aggressive disease and anti-tumor activity of the drug against PSMA expressing lesions may provide clinical benefit even in the presence of PSMA-negative lesions. Assessment of efficacy and safety of patients with at least one PSMA-expressing lesion who did not meet the ^{68}Ga-PSMA-11 PET-based selection criteria but had at least one positive PSMA expressing lesion will serve as a PMC.

8.2. Review of Safety

The Applicant's Position:

The safety evaluation included all subjects who received at least one dose of randomized study treatment (FAS Safety Analysis set). The safety assessment of ^{177}Lu-PSMA-617 (7.4 GBq)+BSC/BSoC is based on data from 529 subjects in the corresponding treatment arm of the registration study PSMA-617-01 (VISION); and 64 patients from the supportive study PSMA-617-02 (RESIST-PC), which were performed in the target indication of mCRPC. 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).
The PSMA-617-01 main study also 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. However, the primary focus is on data from 529 subjects treated with at least one dose of study drug in the PSMA-617-01 study.
In PSMA-617-01 study, the safety of ^{177}Lu-PSMA-617 was also evaluated across relevant patient subgroups including subgroups with and without NAADs at baseline, according to the numbers 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.
Data from the PSMA-617-01 study allows for a comprehensive and informed assessment of the safety profile of the ^{177}Lu-PSMA-617+BSC/BSoC combination and an evaluation of the overall benefit-risk in adult patients with PSMA-positive mCRPC. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management in the intended population; hence only data from PSMA-617-01 is being discussed in the following sections.

The FDA's Assessment:
The primary basis of FDA's safety review is the VISION trial. No data from trial RESIST-PC were analyzed during review of this application due to differences in patient populations and the limited number of patients enrolled in RESIST-PC.

8.2.1. Safety Review Approach

The Applicant's Position:
The data presented here is a comprehensive analysis of safety data relevant to the use of ^{177}Lu-PSMA-617 in combination with BSC/BSoC in the treatment of adult patients with PSMA-positive mCRPC.
Based on the mechanism of action (from published dosimetry study results and clinical observations), the main expected toxicities of ^{177}Lu-PSMA-617 are 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), 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).

Clinical experience with ^{177}Lu-PSMA-617 administered as a single agent, in combination with BSC/BSoC, confirm that these events are some of the most frequent toxicities observed with ^{177}Lu-PSMA-617. 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.

The FDA's Assessment: The median (range) duration of follow-up (from randomization to death due to any cause or date of last contact) for patients in the FAS safety analysis set (N=734) was 14.13 (0.6-31.5) months. A longer duration of follow up is required for adequate assessment of potential delayed toxicities due to radiation exposure.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Extent of exposure: For the purposes of this safety analysis, exposure to study treatment in Study PSMA-617-01 was considered appropriate to allow for an adequate assessment of safety in subjects who were representative of the intended target population. Hence, data from the Study PSMA-617-01 is being discussed here.

In Study PSMA-617-01, the median duration of exposure to randomized treatment was longer in the ^{177}Lu-PSMA-617+BSC/BSoC arm (7.8 months) compared to BSC/BSoC only arm (2.1 months) (Table 26).

In the ^{177}Lu-PSMA-617+BSC/BSoC arm, 46.5% of the patients received 6 cycles of ^{177}Lu-PSMA-617, the maximum number of cycles planned per protocol, and 67.7% received at least 4 cycles, the minimum recommended per protocol. The mean dose intensity was 5.5 (SD ±1.2) GBq/month, and the mean cumulative dose was 33.4 GBq (SD ±12.8) (Table 27).

Table 26: 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

Table 27: 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)

[1] n=93
A patient may be counted in more than one row for reason for delay of cycle.
^{177}Lu-PSMA-617 cycles are once every 6 weeks for a maximum of 6 cycles.

The FDA's Assessment:
FDA agrees with the Applicant's position on duration of exposure to randomized treatments, duration of 177Lu-PSMA-617 exposure in PSMA-617-01 and summary of cycles.

Relevant characteristics of the safety population:
The Applicant's Position:
In the PSMA-617-01 study, per the inclusion criteria, patients had received at least one NAAD (i.e. abiraterone acetate or enzalutamide) and at least one but no more than 2 previous taxane-based chemotherapy regimens. Only patients with at least one PSMA-positive lesion identified on ^{68}Ga-PSMA-11 PET/CT scan and no PSMA-negative lesions fulfilling the exlusion criteria (as

assessed by an independent central reader) were to be enrolled in the study, provided all other inclusion/exclusion criteria were met. An independent central review was utilized to ensure consistency in patient selection as described by the central read rules.

The safety of ^{177}Lu-PSMA-617 was also evaluated across relevant patient subgroups. See Section 8.2. Demographic characteristics were well balanced between the two treatment arms (^{177}Lu-PSMA-617+BSC/BSoC), thereby providing reassurance with regard to the interpretation of the treatment comparison and the validity of the safety conclusions. Overall, the baseline characteristics were representative of the broad population of subjects with mCRPC (Table , Table).

The FDA's Assessment:
FDA agrees with the Applicant's characterization of the eligible population in VISION.

Patients from non-white races were underrepresented in this clinical trial. Additionally, patients with severe renal impairment (GFR <30) were excluded from VISION.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data from the registration study (Study PSMA-617-01). Further details are provided in different subsections of Section 8.2.

With respect to doses received, duration of treatment, patient demographics, and disease characteristics, this population allows for an informed assessment of the safety profile of ^{177}Lu-PSMA-617+BSC/BSoC and a judgment of the overall benefit-risk in patients with mcRPC.

The FDA's Assessment:
The duration of follow up at the time of this review was not adequate to allow for a reliable characterization of potential long-term toxicities in patients receiving the investigational agent. This is discussed further below.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site

inspections by the Sponsor; data in the CRFs and AE databases were consistent.

The FDA's Assessment:
There was no concerning issue regarding integrity and quality of the submitted data.

Categorization of Adverse Events

In Study PSMA-617-01, randomized treatment was evaluated for the following:

- Frequency, type (by system organ class (SOC) and preferred term (PT)), severity, and causal relationship of AEs to study drug
- Deaths, frequency of SAEs, AESI, AEs leading to discontinuation, and AEs requiring dose reduction and/or interruption

All AEs were coded using MedDRA version 23.1 and graded using NCI CTCAE version 5.0 for Study PSMA-617-01. In tables of summaries of AEs, a patient with multiple grades for an AE is only counted once under the maximum grade. In addition to the safety evaluations outlined above, several AE categories warranting closer scrutiny were identified during the development program, based either on the mechanism of action of ^{177}Lu-PSMA-617 and biological plausibility, on nonclinical observations, or as standard safety topics.

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

The FDA's Assessment:
FDA review focused on observed adverse events regardless of attribution by the investigator.

The following adverse reactions are grouped terms (all other events noted are single PT terms):

"Peripheral edema" includes peripheral edema, fluid retention, and fluid overload.

"Dry mouth" includes dry mouth, aptyalism, and dry throat.

"Vomiting" includes vomiting and retching.

"Abdominal pain" includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

"Urinary tract infection" includes urinary tract infection, cystitis, and cystitis bacterial.

"Acute kidney injury" includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

"Dysgeusia" includes dysgeusia and taste disorder.

"Hemorrhage" includes haematuria, lower gastrointestinal haemorrhage, haemorrhage intracranial, haematemesis, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, rectal haemorrhage, cerebral haemorrhage, gastric haemorrhage, haemoptysis, epistaxis.

"Musculoskeletal pain" includes back pain, bone pain, neck pain, arthralgia, spinal pain, pain in extremity.

"Sepsis" includes sepsis, urosepsis, septic shock, bacterial sepsis, escherichia sepsis, klebsiella sepsis.

"Urinary tract infection" includes urinary tract infection, pyelonephritis acute.

"Pneumonia" includes pneumonia, pneumonia aspiration, lower respiratory tract infection.

"Pancytopenia" includes pancytopenia, bicytopenia, bone marrow failure.

"Hepatic failure" includes acute hepatic failure and hepatic failure.

Routine Clinical Tests

Regular monitoring of hematology and clinical chemistry, urinalysis, and assessment of vital signs was performed. Data from all sources (local laboratories) were combined. The summaries included all laboratory assessments collected no later than 30 days after randomized treatment discontinuation.

During long-term follow-up, limited safety data were collected (hematology, blood chemistry, and AE assessment). The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with ^{177}Lu-PSMA-617+BSC/BSoC.

The FDA's Assessment:
FDA agrees with the Applicant's description of clinical and laboratory monitoring of patients for adverse reactions..

8.2.4. Safety Results

Deaths

The Applicant's Position:

Overall, 463 patients in the FAS safety analysis set died during the study, and 85 patients died while on-treatment: 66 (12.5%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 19 (9.3%) in the BSC/BSoC only arm. In both arms, the most frequent primary cause for death was disease progression (8.3% in the ^{177}Lu-PSMA-617+BSC/BSoC arm and 6.8% in the BSC/BSoC only arm).

A review of the deaths in Study PSMA-617-01 did not identify any pattern as most subjects who died had underlying contributing comorbidities and complications associated with their disease. Most deaths were due to disease progression (Table 28).

Table 28: Summary of On-treatment Deaths 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 (%)**
Total Deaths	321 (60.7)	142 (69.3)
Disease progression	244 (46.1)	100 (48.8)
Adverse event	25 (4.7)	13 (6.3)
Unknown	43 (8.1)	21 (10.2)
Other	8 (1.5)	6 (2.9)
Due to COVID-19	1 (0.2)	2 (1.0)
On-treatment Deaths [1]	**66 (12.5)**	**19 (9.3)**
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.

SAEs leading to a fatal outcome

SAEs leading to fatal outcome during randomized treatment are being discussed here.

Per protocol, disease progression was not to be reported as an AE leading to fatal outcome, however this was not fully clarified before implementation of amendment 3, and 2 such SAEs (presented in the table of SAEs with fatal outcome) were reported by the investigators (one in each arm) before protocol clarification.

COVID-19 was reported as a SAE leading to fatal outcome, while for the on-treatment death the patient who died of COVID-19 is not counted in the death due to "AE".

Twenty-five patients had SAEs with fatal outcomes, 19 (3.6%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm (including 1 disease progression and 1 "COVID-19") and 6 (2.9%) in the BSC/BSoC only arm (including 1 disease progression). The only events that were reported more than once in either arm were sepsis (4 patients, 0.8%) and pancytopenia (2 patients, 0.4%), all of which were reported in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

Death as an outcome of an AE considered by the investigator to be at least possibly related to study medication was reported in 5 patients (0.9%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm and in none in the BSoC-only arm. These five fatal events were the following: pancytopenia (2), bone-marrow failure (1), subdural hematoma (1), intracranial hemorrhage (1). The cases of pancytopenia and bone marrow failure were complicated by progressive cancer and bone marrow involvement at baseline. Cases of intracranial hemorrhage, including subdural hematoma, were of low number in the PSMA-617-01 study overall and were balanced between the treatment arms.

AEs leading to fatal outcomes during long-term follow-up

The Applicant's Position:

Seven patients in each arm had an AE with a fatal outcome. There was no apparent cluster in either arm.

The FDA's Assessment:

Fatal adverse reactions occurred in 2.8% of patients who received ^{177}Lu-PSMA-617 plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%).

^{177}Lu-PSMA-617's effect on the bone marrow has demonstrated myelosuppression, as discussed further below. Notably, 3 patients experienced a fatal adverse event that was associated with concomitant myelosuppression in one or more cells lines that likely contributed to the death. Two deaths due to bleeding (intracranial hemorrhage and subdural hematoma) occurred in patients who had concurrent thrombocytopenia. One death due to sepsis occurred in a patient with concurrent neutropenia.

Overall, death rates between arms were comparable and there was not an unexpectedly higher death rate in the ^{177}Lu-PSMA-617 arm compared to the control group.

Serious Adverse Events

The Applicant's Position:

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 SAEs. In keeping with the overall TEAEs, the number of patients who had SAEs, including high grade SAEs (grade ≥3) were generally more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

The incidence of SAEs by SOCs (for the majority of SOCs) was generally higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Overall, the SOCs with SAEs 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).

The incidence of SAEs and high grade SAEs (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). 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 SAEs, as determined by the Investigator. The incidence of drug-related SAEs, and high grade serious TEAEs (grade ≥3) were relatively low (<3.0% patients) in both arms.

The FDA's Assessment: Serious adverse reactions occurred in 36% of patients who received ^{177}Lu-PSMA-617 plus BSoC. Serious adverse reactions in >1% of patients who received ^{177}Lu-PSMA-617 plus BSoC included hemorrhage (4.0%), musculoskeletal pain (3.8%), sepsis (3.2%), anemia (2.8%), urinary tract infection (2.6%), acute kidney injury (1.7%), pneumonia (1.7%), pancytopenia (1.3%), pyrexia (1.3%), spinal cord compression (1.1%), and pulmonary embolism (1.1%).

Overall, a higher number of SAEs occurred in the ^{177}Lu-PSMA-617 arm compared to the BSC arm. Several patients had hemorrhage with concomitant thrombocytopenia (n=16, including 8 with an SAE of hemorrhage) or an infection in the setting of neutropenia (n=14, including 4 SAE of infection), which they may have been predisposed to due to the myelosuppressive effect of ^{177}Lu-PSMA-617. Overall, no new safety signals were identified upon review of SAEs in VISION.

Dropouts and/or Discontinuations

A summary of treatment discontinuations as reported by the investigator is presented in Table 29. 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).

The reasons for discontinuation of BSC/BSoC 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 (42.3% patients vs. 35.6% patients); AEs (5.5% patients vs. 2.0% patients); no longer clinically benefiting (13.6% patients vs. 24.4% patients); and withdrew consent for treatment (9.5% patients vs. 18.0% patients).

Table 29: Summary of Treatment Discontinuation 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 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)

Dropouts and/or Discontinuations Due to Adverse Effects

Permanent discontinuation of ^{177}Lu-PSMA-617 due to AEs

Permanent discontinuation of ^{177}Lu-PSMA-617 due to AEs are presented in Table 30. The most frequent events were related to cytopenias (from 2.8% for thrombocytopenia and anemia to 0.6% for pancytopenia). All other events were reported in less than 0.5% of the patients each.

Table 30: AEs leading to permanent discontinuation of ^{177}Lu-PSMA-617 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
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

Permanent discontinuation of BSC/BSoC due to AEs

The Applicant's Position:

These events were infrequent, each observed in ≤ 1.0% of the patients in either arm, except for spinal cord compression which was reported in 1.5% of patients in the BSC/BSoC only arm (vs. none in the ^{177}Lu-PSMA-617+BSC/BSoC arm).

The FDA's Assessment:

FDA agrees with the Applicant's description of dropouts and treatment discontinuations. . More patients in the ^{177}Lu-PSMA-617 arm discontinued therapy due to an adverse event compared to the BSC arm. This is not unexpected, as patients receiving ^{177}Lu-PSMA-617 in addition to BSC would be at a higher risk of developing more toxicities from both ^{177}Lu-PSMA-617 and the BSC than patients only receiving BSC.

The BSC arm had considerably more dropout due to withdrawal of consent, as already noted in other sections of this review.

Dose Interruption/Reduction Due to Adverse Effect

AEs leading to dose reduction or interruption during randomized treatment

AEs leading to dose interruption or reduction of ^{177}Lu-PSMA-617: AEs leading to dose interruption and AEs leading to dose reduction of ^{177}Lu-PSMA-617 are presented in Table 31. Of note, AEs that led to dose interruption presented in this summary table include AEs that caused the patient to miss a scheduled dose. The most frequent events 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 that led to dose interruption or reduction were reported for less than 2.0% of the patients.

Table 31: AEs leading to interruption or reduction of ^{177}Lu-PSMA-617 occurring in at least 0.5% of the patients during randomized treatment (FAS safety analysis set)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
AEs leading to interruption of ^{177}Lu-PSMA-617		
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)

	^{177}Lu-PSMA-617+BSC/BSoC N=529	
Preferred term	**All grades n (%)**	**Grade ≥ 3 n (%)**
Neutropenia	4 (0.8)	1 (0.2)
Aspartate aminotransferase increased	3 (0.6)	1 (0.2)
Haematuria	3 (0.6)	2 (0.4)
AEs leading to reduction		
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)

AEs leading to dose interruption or reduction of BSC/BSoC: These events were infrequent in both arms (< 2.0% for any event).

The Applicant's Position:
The most frequent AEs 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).

The FDA's Assessment:
FDA agrees with the Applicant's description of adverse reactions leading to dose reduction or interruption. The most frequent AEs leading to dose interruption or reduction of ^{177}Lu-PSMA-617 were hematologic (anemia, thrombocytopenia). These events are the result of ^{177}Lu-PSMA-617's myelosuppressive effect on the bone marrow. Patients with metastatic CRPC often have diffuse bone metastatic disease that can infiltrate the bone marrow and the population enrolled in VISION had also received prior treatment with taxane chemotherapy. Both of these factors further predispose pateints to potential hematologic toxicity due to decreased bone marrow reserve.

Of patients receiving ^{177}Lu-PSMA-617 who had a dose reduction, evaluation of baseline creatinine clearance in these patients noted that 9 patients (30%), 14 patients (47%), and 7 patients (23%) had normal, mild, or moderate baseline CrCl per Cockcroft-Gault method categories. No patients had severe renal impairment at baseline.

Significant Adverse Events

The Applicant's Position:

The significant AEs reported are described in other sections of this document.

Treatment Emergent Adverse Events and Adverse Reactions

In the Study PSMA-617-01, the treatment-emergent period was defined as the period from the date of initiation of study 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. AEs events were subsequently collected in the long-term follow-up as self-reported AEs, recorded only with event term and severity.

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. This imbalance in the treatment duration of exposure should be considered when comparing the AE incidence rates between the 2 treatment arms.
The greatest differences (≥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

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 greatest differences (≥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 further details on discontinuations described in the sections above.
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 32.

Table 32: 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)

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.

Adverse events during 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-treatment visit for a duration of 24 months or until 508 deaths (whichever occurred first). See Section 8.1.1. The incidence of AEs and high grade AEs (≥3) were similar for both the groups of patients, ie, the incidence of AEs 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.

ADRs
ADRs are listed by MedDRA system organ class (Table 33). The most ADRs (≥ 20%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSC/BSoC only arm include: fatigue (43%), dry mouth (39%), nausea (35%), anemia (32%), decreased appetite (21%), and constipation (20%). The most common Grade 3 to 4 adverse reactions (≥ 5%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSC/BSoC only include: anemia (13%), thrombocytopenia (8%), lymphopenia (8%), and fatigue (6%.

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Table 33: ADRs occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSoC alone in PSMA-617-01[a]

Adverse Reactions*	^{177}Lu-PSMA-617+BSC/BSoC (N = 529)		BSC/BSoC (N = 205)	
	All Grades (%)	Grades 3 to 4[b] (%)	All Grades (%)	Grades 3 to 4 (%)
Blood and lymphatic system disorders				
Anemia	32	13	13	4.9
Thrombocytopenia	17	8	4.4	1
Leukopenia[c]	16	4.2	2	0.5
Lymphopenia	14	8	3.9	0.5
Pancytopenia[d]	1.7	1.3[b]	0	0
Nervous system disorders				
Dizziness	8	0.9	4.4	0
Headache	7	0.8	2	0
Dysgeusia[e]	7	0	1.5	0
Eye disorders				
Dry eye	3	0	1	0
Ear and labyrinth disorders				
Vertigo	2.1	0	0	0
Gastrointestinal disorders				
Dry mouth[f]	39	0	0.5	0
Nausea	35	1.3	17	0.5
Constipation	20	1.1	11	0.5
Vomiting[g]	19	0.9	6	0.5
Diarrhea	19	0.8	2.9	0.5
Abdominal pain[h]	11	1.1	6	0.5
Renal and urinary disorders				
Urinary tract infection[i]	12	3.8	1	0.5
Acute kidney injury[j]	9	3.2	6	2.9
General disorders and administration site conditions				
Fatigue	43	6	23	1.5
Decreased appetite	21	1.9	15	0.5

Adverse Reactions*	^{177}Lu-PSMA-617+BSC/BSoC (N = 529)		BSC/BSoC (N = 205)	
	All Grades (%)	Grades 3 to 4[b] (%)	All Grades (%)	Grades 3 to 4 (%)
Weight decreased	11	0.4	9	0
Peripheral edema[k]	10	0.4	7	0.5
Pyrexia	7	0.4	3.4	0

* All the numbers have been rounded up
[a]National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
[b]Only includes Grades 3 to 4 adverse reactions, with the exception of pancytopenia. Grade 5 (fatal) pancytopenia was reported in 2 patients who received ^{177}Lu-PSMA-617+BSC/BSoC.
[c]Leukopenia includes leukopenia and neutropenia.
[d]Pancytopenia includes pancytopenia and bicytopenia.
[e]Dysgeusia includes dysgeusia and taste disorder.
[f]Dry mouth includes dry mouth, aptyalism, and dry throat.
[g]Vomiting includes vomiting and retching.
[h]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.
[i]Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.
[j]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.
[k]Peripheral edema includes peripheral edema, fluid retention, and fluid overload

The FDA's Assessment:

The most common adverse reactions (≥ 20%) occurring at a higher incidence in patients who received ^{177}Lu-PSMA-617 plus BSoC were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation.

Adverse events of special interest include hematologic toxicity (e.g. neutropenia, anemia, thrombocytopenia) and myelosuppression, acute kidney injury, dry eye, and dry mouth. These events were expected based on ^{177}Lu-PSMA-617's mechanism of action, with radiation absorbed to these sensitive target organs causing these events. All of these events were noted to be higher in the ^{177}Lu-PSMA-617 arm compared to the BSC only arm. These events are discussed in more detail in Section 8.2.5

FDA review also evaluated fracture events. The review team grouped together all AEs which included the word "fracture" in the PT and there was no remarkable difference between arms.

Table 34. Summary of treatment emergent fractures by PT and grade in patients who received ^{177}Lu-PSMA-617+BSC/BSoC compared to BSoC alone in PSMA-617-01[a] in the FAS Safety Set.

TEAE	Lu-PSMA-617 +BSC/BSoC N=529		BSC/BSoC only N=529	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
All treatment emergent fractures	**31 (5.9)**	**11 (2.1)**	**8 (3.9)**	**1 (0.5)**
Spinal compression fracture	8 (1.5)	2 (0.4)	1 (0.5)	0 (0.0)
Hip fracture	5 (0.9)	2 (0.4)	0 (0.0)	0 (0.0)
Pathological fracture	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)
Rib fracture	3 (0.6)	0 (0.0)	3 (1.5)	1 (0.5)
Foot fracture	2 (0.4)	0	0 (0.0)	0
Pelvic fracture	2 (0.4)	0	0 (0.0)	0
Spinal fracture	2 (0.4)	2 (0.4)	1 (0.5)	0 (0.0)
Tooth fracture	2 (0.4)	0	1 (0.5)	0
Acetabulum fracture	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Femoral neck fracture	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Femur fracture	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Lower limb fracture	1 (0.2)	0	1 (0.5)	0
Thoracic vertebral fracture	1 (0.2)	0	1 (0.5)	0
Hand fracture	0 (0.0)	0	1 (0.5)	0

At the request of the FDA, the Applicant provided an analysis of prior RT or additional RT during treatment with ^{177}Lu-PSMA-617 and association with an increased risk of AEs. The majority of patients had received prior RT in their medical history (76% in the ^{177}Lu-PSMA-617 arm). These patients had a slightly higher rate of serious TEAEs compared to those who had not received prior RT (38% vs. 31%) and of grade 3-5 TEAEs (55% vs. 47%). The AEs that appeared more frequent in the prior RT group included diarrhea, lymphopenia, asthenia, hypertension, blood creatinine increased, muscular weakness, hot flush, muscle spasms, neck pain, and rash. Notably, anemia, thrombocytopenia, leukopenia, and neutropenia were similar or more common in the non-prior RT group. This analysis demonstrates that prior or concurrent RT may be associated with a slightly higher likelihood of experiencing a serious or higher grade events on ^{177}Lu-PSMA-617, but no specific safety risk was identified.

At the request of the FDA, the Applicant provided information on patients who received subsequent additional radiopharmaceuticals. Fifteen patients in the ^{177}Lu-PSMA-617 arm and 16 patients in the BSC arm received a post-treatment radiopharmaceutical, and adverse events between arms in these patients were similar.

During the review, the FDA requested that the Applicant perform additional analyses to explore the relationship between safety outcomes and baseline body weight and disease burden in patients who received ^{177}Lu-PSMA-617 in VISION. Disease burden was defined as the volume of segmented PSMA positive tumor (PSMA + tumor volume) in the whole body using ^{68}Ga-PSMA-11 PET imaging. Disease burden was categorized as <median value of PSMA + tumor volume in the whole body vs ≥median value. The median PSMA + tumor volume in the whole body was derived using all patients randomized to the ^{177}Lu-PSMA-617 + BSoC/BSC arm who had good quality images available. The analysis of rPFS and OS by baseline body weight and PSMA-positive tumor volume in the whole body are presented in the table below. The summary of adverse events by body weight and PSMA-positive tumor volume (cc) in whole body (FAS safety set) are shown in table below.

Table 35. Overview of adverse events by body weight (BW) and PSMA-positive tumor volume (TV) (cc) in whole body (FAS safety set)

	BW <80 kg		BW ≥ 80 kg		All patients	
	TV < 398.144 cc (N=100)	TV ≥ 398.144 cc (83)	TV < 398.144 cc (N=166)	TV ≥ 398.144 cc (N=162)	TV < 398.144 cc (N=272)	TV ≥ 398.144 cc (N=254)
Treatment-emergent adverse events (TEAE)	96 (96%)	81 (98%)	162 (98%)	162 (100%)	264 (97%)	252 (99%)
Serious TEAE	37 (37%)	32 (39%)	44 (27%)	71 (44%)	83 (31%)	108 (43%)
Grade 3 to 5	47 (47%)	51 (61%)	69 (42%)	98 (61%)	121 (46%)	157 (62%)
Drug-related TEAE	83 (83%)	70 (84%)	141 (85%)	141 (87%)	229 (84%)	220 (87%)
Drug-related grade 3 to 5 TEAE	23 (23%)	34 (41%)	32 (19%)	53 (33%)	58 (21%)	91 (36%)
TEAE leading to dose reduction of ^{177}Lu-PSMA-617	6 (6%)	11 (13%)	9 (5%)	19 (12%)	16 (6%)	32 (13%)
TEAE leading to dose interruption of ^{177}Lu-PSMA-617	15 (15%)	13 (16%)	15 (9%)	37 (23%)	31 (11%)	53 (21%)
TEAE leading to discontinuation of ^{177}Lu-PSMA-617	8 (8%)	13 (16%)	14 (8%)	25 (15%)	23 (9%)	40 (16%)
Fatal TEAE	4 (4%)	4 (4.8%)	3 (1.8%)	8 (4.9%)	7 (2.6%)	12 (4.7%)

The results of this safety analysis demonstrated that TEAEs occurred in higher frequency in patients with higher tumor volume. However, no substantial differences were noted with respect to SAEs, grade 3 to 5 events, or fatal adverse events. The interpretation of these data are limited, as patients with more tumor volume may experience more disease-related symptoms from the increased tumor burden rather than the treatment.

On October 27th, 2021, the Applicant submitted the 90-day safety update report. The 90-day safety update report included data on 734 patients from the PSMA-617-01 main study and 30

patients from the PSMA-617-01 sub-study with data cut-off date of June 28, 2021. This provided five additional months of safety follow up. No substantial differences in the safety data in patients receiving ^{177}Lu-PSMA-617 between the original and the updated safety reports were noted and the 90-day safety update did not change the primary interpretation of the safety data or identify any new safety signals. To better assess the delayed toxicities of radiation, a longer duration of follow up is required.

Laboratory Findings

Hematology abnormalities

Worst post-baseline hematology abnormalities during randomized treatment are presented in Table 36. Hematology abnormalities were more frequent in the ^{177}Lu-PSMA-617+BSC/BSoC arm for parameters such as low lymphocytes level (50.9% vs. 19.0% grade 3/4 abnormalities), anemia (15.1% vs. 6.3% grade 3/4 abnormalities) and low platelets (9.3% vs. 2.4% grade 3/4 abnormalities). It should be noted that anemia, lymphopenia or thrombocytopenia that led to permanent discontinuation remained infrequent events (< 3.0% each) and were observed with similar incidences in both treatment arms during randomized treatment.

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).

Table 36: Worst post-baseline hematology abnormalities based on CTC grades during randomized treatment (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

Biochemistry abnormalities

Worst post-baseline biochemistry abnormalities during randomized treatment are presented in Table37. Biochemistry values observed during randomized treatment were similar in both arms. In both arms, grade 3/4 abnormal levels were infrequent events (< 3.0%).

For both arms and all parameters analyzed, almost all patients had normal (grade 0) or low grade abnormalities (grade 1 or 2) at baseline. During treatment, only few shifts to higher grades were observed.

Table37: Worst post-baseline biochemistry abnormalities based on CTC grades during randomized treatment (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)
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

The Applicant's Position:

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

The FDA's Assessment:

FDA agrees with the Applicant's position. The most common laboratory abnormalities that worsened from baseline in ≥ 30% of patients who received ^{177}Lu-PSMA-617 were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium. The following table summarizes select laboratory abnormalities that worsened from baseline.

Table 38: Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients With PSMA-positive mCRPC Who Received ^{177}Lu-PSMA-617 Plus BSoC (Between Arm Difference of ≥ 5% All Grades) in VISION

Laboratory Abnormalities	^{177}Lu-PSMA-617 Plus BSoC[a]		BSoC[b]	
	All Grades (%)	Grades 3 to 4 (%)	All Grades (%)	Grades 3 to 4 (%)
Chemistry				
Decreased calcium	39	2.5	28	3
Decreased sodium	33	0.6[c]	23	1
Increased aspartate aminotransferase	28	1.1	18	1[c]
Increased creatinine	24	0.9[c]	14	0.5[c]
Increased potassium	24	0.6	18	0.5[c]
Increased sodium	11	0[c]	5	0[c]
Hematology				
Decreased lymphocytes	85	47	51	18
Decreased hemoglobin	63	15[c]	34	7[c]
Decreased leukocytes	56	7	22	2
Decreased platelets	45	9	20	2.5
Decreased neutrophils	28	4.5	9	0.5

Abbreviation: BSoC, best standard of care.
[a] The denominator used to calculate the rate for each laboratory parameter varied from 506 to 529 based on the number of patients with a baseline value and at least one post-treatment value.
[b] The denominator used to calculate the rate for each laboratory parameter varied from 194 to 198 based on the number of patients with a baseline value and at least one post-treatment value.

[c] **No Grade 4 laboratory abnormalities worsening from baseline were reported.** The most common laboratory abnormalities that worsened from baseline were hematologic parameters. As discussed in several other sections of this review, hematologic toxicity was anticipated due to the mechanism of action of ^{177}Lu-PSMA-617 and may have been exacerbated by baseline patient characteristics (e.g. extensive bony metastatic disease, receipt of prior systemic chemotherapy, etc.).

Vital Signs

The Applicant's Position:
Notable vital signs were typically observed in < 10.0% of the patients, except for decreased

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

The FDA's Assessment:
FDA agrees with the Applicant's summary of notable changes in vital signs.

Electrocardiograms (ECGs) and QT

Applicant Position:
ECG was performed at screening only for the main PSMA-617-01 study; however, a systematic collection of ECG data at baseline and after treatment with ^{177}Lu-PSMA-617+BSC/BSoC was made in the PSMA-617-01 sub-study. For the cardiodynamic evaluation in the sub-study, 12-lead ECGs and PK samples were collected on Cycle 1 Day 1 prior to the administration of ^{177}LuPSMA-617 and at 1, 4, and 24 hours post-dose. ^{177}LuPSMA-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.

The primary and secondary analyses demonstrated no clinically relevant effects of ^{177}Lu-PSMA-617 on QTcF. In the by-timepoint analysis, LS mean change-from-baseline QTcF (ΔQTcF) on ^{177}Lu-PSMA-617 ranged from -5.2 to 2.1 ms. In the concentration-QTc analysis, the predicted QT effect (ΔQTcF) for ^{177}Lu-PSMA-617 (geometric mean C_{max} 3.8 ng/mL) was 3.12 ms (2-sided 90% upper confidence bound 5.5 ms). Based on this concentration-QTc analysis, an effect on ΔQTcF exceeding 20 ms can be excluded within the full range of observed ^{177}Lu-PSMA-617 plasma concentrations (up to ~6 ng/mL).
Cinically relevant QTc prolongation was not observed in this trial, however the data are limited due to the first ECG-PK pair having been collected 1 hour after the end of infusion, rather than during or immediately after. Therefore, due to limitations of the sampling frequency, a small QTcF increase occurring during the drug infusion or shortly after the end of infusion cannot be excluded, though concentration-QTc modeling predicts a maximal mean QTcF increase below 9 ms. The true T_{max} likely occurred during the infusion or slightly thereafter at which C_{max} was measured to be 6.58 ng/mL by non-compartmental analysis. It is uncommon to observe the largest QTc increase exactly at T_{max} since most QTc prolonging drugs interact with the hERG encoded IKr channel at the intracellular side of the pore, and binding kinetics are thus governed by intracellular concentration, which typically lags behind plasma concentration. However, the concentration-QTc model predicted a mean QTcF increase of 8.6 ms (90% UCI 13.6 ms) at a plasma concentration of 6.58 ng/mL, suggesting that ^{177}Lu-PSMA-617 has at most a minimal effect on QTc at the clinical dose. Using on compartmental analysis, the $t_{1/2}$ for the rapid phase of ^{177}Lu-PSMA-617 elimination is 1-2 hours. This would suggest that, if present, any QTc increase would be very transient.

Based on a comprehensive analysis of the clinical ECG data from the PSMA-617-01 sub-study, the negative preclinical results in cardiovascular safety studies, and the lack of clinical findings related to QT prolongation in study PSMA-617-01, ^{177}Lu-PSMA-617 administration poses a low likelihood of a QTc-related cardiac risk.

The FDA's Assessment:
The FDA Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviewed the Applicant's clinical pharmacology and cardiac safety studies and the Cardiac Safety Report. No large QTcF prolongation effect (i.e., >20 msec) of ^{177}Lu-PSMA-617 was observed in an alternative design to a thorough QT study. It is not possible to draw conclusions of a lack of an effect in the absence of a positive control or data characterizing the QTc response at a sufficiently high multiple of the clinically relevant exposure.

Immunogenicity

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA has no additional comments.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no 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. The four most relevant safety topics are discussed here:

Myelosuppression: based on the sensitivity of the bone marrow to radiation effects, this is considered a known risk for ^{177}Lu-PSMA-617, and data from the PSMA-617-01 sub-study showed that the mean absorbed radiation dose for ^{177}Lu-PSMA-617 in the red marrow was 0.035±0.020 Gy/GBq. The frequency of myelosuppression-related events (including anemia, thrombocytopenia, lymphopenia, leukopenia, neutropenia) was higher in the ^{177}Lu-PSMA-617+BSC/BSoC arm (47.4% of patients) compared with the BSC/BSoC only arm (17.6% of patients). High grade (≥3) events of myelosuppression were higher in the 177Lu-PSMA-617+BSC/BSoC arm (23.4% patients vs. 6.8% patients), as were the SAEs (5.1% patients vs. 0.5% patients). Myelosuppression related events leading to withdrawal of ^{177}Lu PSMA-617 were frequent (7.0% patients).

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 both resolve and recur. 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.

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

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

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

Dry Eye: Dry eye was reported by 16 patients (3.0%) in the ^{177}Lu-PSMA-617+BSC/BSoC arm, and 2 patients (1.0%) in the BSC/BSoC only arm. These were all grade 1 events, except for 1 grade 2 event in 1 patient in the ^{177}Lu-PSMA-617+BSC/BSoC arm. Grade 1 events were defined as asymptomatic where lubricants were sufficient (as per CTCAE v5.0). Three patients (0.6%) received artificial tears as concomitant medication. Grade 2 events were defined as symptomatic with moderate decrease in visual acuity (as per CTCAE v5.0). The single grade 2 event occurred in an 89-year-old patient on study day 158, and was still ongoing at the latest observation. The patient had no other eye- or vision-related AEs. Overall, the analysis shows that dry eye is an infrequent event for patients on ^{177}Lu-PSMA-617 treatment, nearly always asymptomatic and manageable with little impact on quality of life.

Renal toxicity: Due to PSMA expression in the proximal tubule, and the known renal route of ^{177}Lu-PSMA-617 excretion, this is also considered a known risk for ^{177}Lu-PSMA-617, and data from the PSMA-617-01 sub-study showed that the mean radiation absorbed dose for the kidneys was 0.43 ± 0.16 Gy/GBq. Renal events were only observed in 8.7% of patients in the ^{177}LuPSMA617+BSC/BSoC arm, and in 5.9% of patients in the BSC/BSoC only arm. Overall, despite higher radiation exposures that may occur in the kidneys of patients treated with ^{177}Lu-PSMA-617, renal toxicity was predominantly low grade comprising creatinine increases that were manageable and reversible.

The Applicant's Position:

Overall, limited and manageable safety-related risks were observed when adding ^{177}Lu-PSMA-617 to BSC/BSoC in heavily pretreated patients with progressive PSMA-positive mCRPC. Events of interest were manageable, often transient allowing continuation of treatment with supportive care, and only caused a few delays in treatment cycles.

The FDA's Assessment:

Myelosuppression:

^{177}Lu-PSMA-617 can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, Grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with ^{177}Lu-PSMA-617 plus BSoC. Grade ≥ 3 pancytopenia occurred in 1.1% (which included two fatal events) in patients treated with ^{177}Lu-PSMA-617 plus BSoC. Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed in patients who received ^{177}Lu-PSMA-617 plus BSoC. One death due to sepsis and concurrent neutropenia were observed in patients who received ^{177}Lu-PSMA-617 plus BSoC.

As noted above in this review, patients with metastatic CRPC often have extensive bony metastatic disease that can potentially compromise bone marrow function. Additionally, the patient population enrolled in VISION received prior taxane-based chemotherapy, which can further decrease bone marrow reserve.

Long term outcomes of myelosuppression, and the potential development of myelodysplastic syndrome and/or acute myeloid leukemia are unknown at this time due to the short follow up duration in VISION. A post-marketing requirement will be issued to further characterize these events. This is discussed further below.

Dry Mouth

Dry mouth occurred more frequently in the ^{177}Lu-PSMA-617 arm. Dry mouth occurred in 39% of patients on ^{177}Lu-PSMA-617 vs. 0.5% in the control arm. No Grade 3-4 events were noted in either arm. The frequency of other oral/dental events was higher in the dry mouth group (9.6%) compared to the non-dry mouth group (5%). These events were mostly low grade and recovered during the study period.

An FDA-requested analysis of correlation with the received cumulative activity of ^{177}Lu-PSMA-617 demonstrated that 157 out of 208 patients (76%) in the dry mouth group received the highest category of >29.6 GBq of ^{177}Lu-PSMA-617 and 56% of patients in the non-dry mouth group received >29.6 GBq. These data suggest that the risk of experiencing dry mouth and the risk of other oral/dental AEs increases with increased ^{177}Lu-PSMA-617 cumulative activity.

Dry Eye

Dry eye occurred in 16 patients (3%) in the ^{177}Lu-PSMA-617 arm. An FDA-requested analysis of correlation with the received cumulative activity of Pluvicto demonstrated that 14 of the 16 patients (87.5%) with dry eye received >29.6 GBq of ^{177}Lu-PSMA-617. Of the patients with no dry eye, 63% also received >29.6 GBq. The number of patients with dry eye and with other ocular events was too low to make any meaningful correlations with cumulative dose activity.

Renal Toxicity:

Acute kidney injury, all grade and grades 3-4, was balanced between arms. However, given its mechanism of action, it is possible that ^{177}Lu-PSMA-617 can cause severe renal toxicity. In the VISION study, Grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with ^{177}Lu-PSMA-617 plus BSoC. Late toxicity due to radiation induced nephrotoxicity is a potential safety issue but the follow up time on VISION was too short in duration to capture this. A post-marketing requirement will be issued to further characterize these events.

Resolution of Adverse Events of Interest:

FDA conducted additional analyses to evaluate the reversibility of adverse events of particular interest. The number and percentage of patients who an unresolved adverse events of interest are summarized in the table below:

Table 39. Outcome of AE Special interest by group term – Treated subjects who experienced at least one selected adverse event from group term

	^{177}Lu-PSMA-617 + BSoC/BSC (N=529)		BSoC/BSC (N=205)	
	All grades n (%)	Not resolved n (%)	All grades n (%)	Not resolved n (%)
Dry mouth	208 (39)	138 (26)	1 (0.5)	1 (0.5)
Anaemia	168 (32)	126 (24)	27 (13)	18 (9)
Thrombocytopenia	91 (17)	74 (14)	9 (4.4)	8 (3.9)
Leukopenia	83 (16)	32 (6)	4 (2)	3 (1.4)
Pancytopenia	10 (1.9)	3 (0.6)	0 (0)	0 (0)
Dysgeusia	37 (7)	28 (5)	3 (1.5)	3 (1.4)
Acute Kidney Injury	21 (4)	6 (1.1)	8 (3.9)	1 (0.5)
Dry eye	16 (3)	9 (1.7)	2 (1)	2 (1.0)

Sources: adsl.xpt,adae.xpt

Grouped terms:

Leukopenia includes leukopenia and neutropenia.

Pancytopenia includes pancytopenia and bicytopenia.

Dysgeusia includes dysgeusia and taste disorder.

Dry mouth includes dry mouth, aptyalism, and dry throat.

Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

Table 40: Proportion of patients with AE of interest whose AE was unresolved at the time of data cut off

	^{177}Lu-PSMA-617 + BSoC/BSC	BSoC/BSC
	Not resolved n (%)	Not resolved n (%)
Dry mouth (GT)	138/208 (66)	1/1 (100)
Anaemia	126/168 (75)	18 (67)
Thrombocytopenia	74/91 (81)	8/9 (89)

	^{177}Lu-PSMA-617 + BSoC/BSC	BSoC/BSC
	Not resolved n (%)	Not resolved n (%)
Leukopenia (GT)	32/83 (39)	3/4 (75)
Pancytopenia (GT) (including bicytopenia)	3/10 (30)	Not evaluable
Dysgeusia (GT)	28/37 (76)	3/3 (100)
Acute Kidney Injury (GT)	6/21 (29)	1/8 (13)
Dry eye	9/16 (56)	2/2 (100)

Overall, several adverse events of interest were noted to be unresolved at the time of the latest data cut-off. Upon further evaluation, however, several patients with anemia, thrombocytopenia, leukopenia, and acute kidney injury had abnormal laboratory values for these parameters at baseline and complete resolution of these events would not be expected. This is further evidenced by similarly high rates of "not resolved" AEs in the BSoC arm. Further follow up is necessary to evaluate whether these events definitively resolve in patients receiving the investigational agent.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Patient-reported outcomes (PRO) have been discussed above in Section 8.1.2.

The FDA's Assessment:
FDA has no additional comment.

8.2.7. Safety Analyses by Demographic Subgroups

In the study PSMA-617-01, subgroup analyses were conducted to identify potential safety issues restricted to particular subpopulations; these typically demonstrated a pattern of events consistent with that reported for the overall study populations.

The safety of ^{177}Lu-PSMA-617 was 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 discussed in detail by the 2 categories of intrinsic factors and extrinsic factors.

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. 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).

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 in medical history, and patients with concurrent radiation therapy in both treatment arms; however, the shifts were more in the ^{177}LuPSMA617+BSC/BSoC arm, probably due to the longer duration of exposure in the ^{177}Lu-PSMA-617+BSC/BSoC arm.

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}LuPSMA-617 compared to those receiving 5-6 cycles. More than 50% of patients randomised to the ^{177}LuPSMA-617+BSC/BSoC arm proceeded to receive 5-6 cycles. Hence, overall, there was no suggestion of a safety concern associated with receiving more cycles of ^{177}LuPSMA-617.

The Applicant's Position:
The subgroup analyses results did not raise any particular safety concerns for any of the subgroups analyzed.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of safety data in patient subgroups, however, a higher incidence of toxicities and dose modifications and dose discontinuations due to toxicities were observed in patients with moderate renal impairment as discussed above. Dosimetry, pharmacokinetics, and safety were not assessed in patients with severe renal impairment. A PMR was issued requiring the Applicant to conduct a clinical trial to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of ^{177}Lu-PSMA-617 and assess the risk of increased toxicities in patients with moderate and severe renal impairment.

Of the 529 patients who received at least one dose of ^{177}Lu-PSMA-617 plus BSoC in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older. Serious adverse reactions occurred in 11% of patients ≥75 years of age and in 11% of younger

patients. Grade ≥3 adverse reactions occurred in 40% of patients ≥75 years of age and in 31% of younger patients.

Overall, no substantial differences in safety were noted among these key subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Within the Phase III PSMA-617-01 study, a dosimetry, pharmacokinetics (PK) and ECG sub-study was also conducted in a non-randomized cohort of ^{177}Lu-PSMA-617+BSC/ BSoC of 30 patients at sites in Germany.
These patients received ^{177}Lu-PSMA-617+BSC/BSoC to provide a more complete assessment of these safety aspects of ^{177}Lu-PSMA-617. Patients in the sub-study were screened for eligibility, treated and followed-up similar to patients in the main study. These patients were not included in the analyses of the randomized part of the study. Relevant results from the sub-study have been discussed in the sections above.

The FDA's Assessment:
FDA agrees with the Applicant's description of the VISION substudy.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
Not Applicable.

The FDA's Assessment:
There was no reported adverse events of MDS/AML or other secondary malignancies in VISION study. However, secondary malignancies are a known adverse event associated with radiation and longer follow up and assessment of a larger population of patients in the post marketing setting is required to assess for the carcinogenicity potential of ^{177}Lu-PSMA-617.

Human Reproduction and Pregnancy
The Applicant's Position:
The safety and efficacy of ^{177}Lu-PSMA-617 have not been established in females as ^{177}Lu-PSMA-617 is not indicated for use in females; therefore, there are no available data on the use of ^{177}Lu-PSMA-617 in pregnant or lactating women. However, based on its mechanism of action, all radiopharmaceuticals, including ^{177}Lu-PSMA-617, can cause fetal harm. 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 was utilized to estimate potential effects on male fertility with ^{177}Lu-PSMA-617 treatment. 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.
Because of its mechanism of action (with radiation being inherently carcinogenic and mutagenic/genotoxic), male patients should use condoms for intercourse during treatment with ^{177}Lu-PSMA-617 and for 14 weeks after the last dose.

The FDA's Assessment:

The safety and efficacy of ^{177}Lu-PSMA-617 have not been established in females. Based on its mechanism of action, ^{177}Lu-PSMA-617 can cause fetal harm. There are no available data on ^{177}Lu-PSMA-617 use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including ^{177}Lu-PSMA-617, have the potential to cause fetal harm.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable

The FDA's Assessment:

FDA has no additional comment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

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 radiation 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 radiation dose that was applied should be estimated.

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.

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

The FDA's Assessment:
FDA agrees with the Applicant's description of overdose, drug abuse potential, withdrawal, and rebound for ^{177}Lu-PSMA-617.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:
^{177}Lu-PSMA-617 has not received marketing authorization in any country.

The FDA's Assessment:
FDA has no additional comment.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse reactions.

The FDA's Assessment:
Post marketing safety data from a larger patient population with longer duration of follow up are required to assess for safety risks and delayed toxicities associated with ^{177}Lu-PSMA-617, particularly radiation-induced radiation toxicites. A post-marketing requirement will be issued to the Applicant to characterize these risks.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Treatment with ^{177}Lu-PSMA-617 in combination with BSC/BSoC is characterized by a predictable and manageable safety profile in patients with progressive PSMA-positive mCRPC. The safety profile in Study PSMA-617-01 was consistent with the mechanism of action of ^{177}Lu-PSMA-617 and as documented in literature in similar populations of patients with mCRPC/ prior clinical experience. AEs reported were typically manageable with appropriate intervention (standard medical care and/or ^{177}Lu-PSMA-617+BSC/BSoC or BSC/BSoC only reduction or treatment interruption), and were mostly transient. Overall, safety was well characterized in the intended target population.

The baseline characteristics of the patients with PSMA-positive mCRPC in the PSMA-617-01 reflect heavily pretreated patients with a high bone and visceral disease burden, which are important aspects to consider while assessing patient toxicities during treatment. Generally, the reported AEs appeared to be predominantly grade 1 or 2 and most frequently reported as salivary gland, hematological, and gastrointestinal toxicities. While the grade ≥ 3 AEs were mainly restricted to hematological events, more AEs were reported in patients receiving ^{177}Lu-PSMA-617+BSC/BSoC (52.7%) vs. those receiving BSC/BSoC only (38.0%); however, the incidence of each grade ≥ 3 AE was low. The most frequent myelosuppression-related AEs were anemia, thrombocytopenia, lymphopenia, leukopenia, and neutropenia, which may be attributed to the effects of ionizing radiation on sensitive precursor cells in circulation or in the bone marrow close to metastatic bone lesions, but which may also be impacted by bone marrow impairment at baseline from prior therapy. The most frequent non-hematologic AEs with ^{177}Lu-PSMA-617 treatment were fatigue, dry mouth, nausea, back pain, arthralgia, decreased appetite, constipation, vomiting, and diarrhea. Most of these (except dry mouth) were nonspecific and attributable to the administration of therapeutic levels of a radioactive compound. Due to PSMA expression in the proximal tubule, and the renal route of excretion, renal effects are considered a risk for ^{177}Lu-PSMA-617. Renal events were only observed in 8.7% of patients in the ^{177}LuPSMA617+BSC/BSoC arm, versus 5.9% of patients in the BSC/BSoC only arm, and consisted predominantly of low grade reversible creatinine increases. Overall, the data show that AEs were manageable and often transient allowing continuation of treatment with supportive care and with only few delays in treatment cycles. The safety of ^{177}Lu-PSMA-617+BSC/BSoC was also evaluated across relevant patient subgroups, and no unexpected differences were observed in any of the subgroups or between the two treatment arms. Overall, a well-tolerated and manageable safety profile was demonstrated for ^{177}Lu-PSMA-617 in heavily pretreated patients with progressive PSMA-positive mCRPC.

The FDA's Assessment:

FDA's integrated assessment of safety focused on the 529 patients with mCRPC who received at least one dose of ^{177}Lu-PSMA-617.

The incidence of all AEs and grade 3-4 AEs was higher in ^{177}Lu-PSMA-617 arm than the control group. Serious adverse reactions occurred in 36% of patients who received 177Lu-PSMA-617. Serious adverse reactions in >1% of patients who received 177Lu-PSMA-617 plus BSoC included

hemorrhage (4.0%), musculoskeletal pain (3.8%), sepsis (3.2%), anemia (2.8%), urinary tract infection (2.6%), acute kidney injury (1.7%), pneumonia (1.7%), pancytopenia (1.3%), pyrexia (1.3%), spinal cord compression (1.1%), and pulmonary embolism (1.1%). Fatal adverse reactions occurred in 2.8% of patients who received 177Lu-PSMA-617 plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%).

177Lu-PSMA-617 was permanently discontinued due to adverse reactions in 12% of patients. Adverse reactions leading to permanent discontinuation of 177Lu-PSMA-617 in ≥1% of patients who received 177Lu-PSMA-617 plus BSoC were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (including neutropenia) (1.7%). Adverse reactions leading to a dose interruption of 177Lu-PSMA-617 occurred in 16% of patients. The most frequent (≥3%) adverse reactions leading to a dose interruption of 177Lu-PSMA-617 in patients who received 177Lu-PSMA-617 were anemia (5%) and thrombocytopenia (3.6%). Adverse reactions leading to a dose reduction of 177Lu-PSMA-617 occurred in 6% of patients. The most frequent (≥1%) adverse reactions leading to a dose reduction of 177Lu-PSMA-617 in patients who received 177Lu-PSMA-617 were thrombocytopenia (1.9%) and anemia (1.3%). The most common adverse reactions (≥ 20%) occurring at a higher incidence in patients who received 177Lu-PSMA-617 were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. The most common laboratory abnormalities that worsened from baseline in ≥ 30% of patients who received 177Lu-PSMA-617 plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

SAEs such as intracranial hemorrhage, subdural hematoma, and sepsis occurred in patints who received ^{177}Lu-PSMA-617 and had concurrent treatment-emergent thrombocytopenia and neutropenia, respectively. Additionally, 2 patients died of grade 5 pancytopenia. All grades and grade 3-4 renal toxicity were higher in ^{177}Lu-PSMA-617 arm than the control arm. However, patients with mild or moderate renal impairment may be at greater risk of toxicity and frequent monitoring of renal function and adverse reactions in patients with mild to moderate renal impairment is needed. The pharmacokinetics and safety of ^{177}Lu-PSMA-617 have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

Adverse events of special interest include hematologic toxicity (e.g. neutropenia, anemia, thrombocytopenia) and myelosuppression, acute kidney injury, dry eye, and dry mouth. These events were expected based on ^{177}Lu-PSMA-617's mechanism of action, with radiation absorbed to these sensitive target organs causing these events. All of these events were noted to be higher in the ^{177}Lu-PSMA-617 arm compared to the BSC only arm. ^{177}Lu-PSMA-617 is a radiactive agent and delayed toxicities of radiation is a concern for this class of drugs. Longer follow up, particularly in earlier disease setting that patients have longer life expectancies, will provide more comprehensive information on radiation-induced delayed toxicities of ^{177}Lu-

PSMA-617.

Overall, the safety profile of ^{177}Lu-PSMA-617 is acceptable for this patient population with an incurable disease in the context of the demonstrated clinically meaningful improvement in OS. Importantly, this product represents a novel systemic treatment with a different toxicity profile than other potential later line treatments.

FDA's expectation is that the safety profile will be further characterized with more data and longer follow up from clinical trials and the postmarket setting. Extended follow-up of patients on VISION study and its sub-study, Trial CAAA617C12301 (NCT04720157), and Trial CAAA617B12302 (NCT04689828) for safety, and assessment of safety of ^{177}Lu-PSMA-617 in patients with moderate or severe renal impairment will be required as PMRs.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The PSMA-617-01 trial demonstrated a statistically significant improvement in OS and rPFS. The secondary endpoint of durable ORR supported these findings. An OS interim analysis was planned at the final rPFS analysis, however, this interim analysis was not performed because the targeted number of final OS events were observed before the targeted number of rPFS events.

Due to early dropout rate among the BSC arm, the Applicant took adequate measures to reduce this effect of dropout by enhancing study site education and communication, as well as capping enrollment at selected sites. Therefore, in order to provide unbiased estimates of the treatment effects, primary analyses used different analysis populations, with OS being analyzed in all randomized patients (N=831) and rPFS being analyzed in patients randomized after these measures were implemented in March 2019 (N=581).

FDA was concerned that asymmetric censoring due to withdrawal of consent and potential informative censoring would impact efficacy results. A variety of conservative and worst-case sensitivity analyses for OS and rPFS were performed to evaluate the disproportionate drop out in the BSoC arm compared to the 177Lu-PSMA-617. Interpretation of rPFS results was limited due to the high degree of censoring, which leads to uncertainty in the estimation of the magnitude of the rPFS treatment effect. Sensitivity analyses were supportive of a robust and statistically persuasive improvement in OS. The conclusion of the statistical review is that the OS results did not appear to be compromised by early dropout.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team recommends regular approval for ^{177}Lu-PSMA-617, 7.4 GBq (200 mCi) every 6 weeks for up to 6 doses for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

The FDA focused its assessment of efficacy on the OS benefit, using rPFS in the modified analysis population as well as durable ORR results from the investigational arm as supportive. In addition to OS being the most clinically important endpoint, loss to follow up of withdrawn patients was mitigated for the OS endpoint by ascertainment of survival status for many patients who withdrew consent, and the overall ITT population was able to be evaluated. The OS benefit was robust, and held up to a series of strict sensitivity analyses reviewed by the FDA statistical team that assessed the impact of remaining asymmetric censoring due to drop out for those whose OS status could not be obtained.

The approval decision took into account several additional contextual factors. Metastatic castration-resistant prostate cancer (mCRPC) is a life threatening condition with lack of curative treatment creating an unmet need. ^{177}Lu-PSMA-617 is a radioactive radioligand therapeutic agent that is the first radioisotope for mCRPC that has demonstrated activity in non-bone areas of disease, providing a novel systemic mechanism of action that may provide an opportunity to be combined with other available therapies with different toxicity profiles across mechanistic classes. In addition to the OS and rPFS findings, additional evidence of efficacy was demonstrated based on durable ORR of 30% with 6% achieiving complete response. Finally, 177Lu-PSMA-617 offers a different safety profile than other available systemic therapies which expands treatment options that can be individualized to a patient's preference and comorbidities.

X _____ X _____

Primary Statistical Reviewer Statistical Team Leader

X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
An advisory committee meeting was not convened for this application.

10 Pediatrics

The Applicant's Position:

On 10-Jun-2019, Endocyte, Inc. received an Agreed Initial Pediatric Study Plan (iPSP) Agreement letter from the Agency, which included a full waiver of pediatric assessments in PSMA-expressing metastatic castration-resistant prostate cancer.

The FDA's Assessment:

Prostate cancer is common in older adults and does not occur in children. Additionally, the activity of ^{177}Lu-PSMA-617 requires the presence of PSMA expression on tumors, which has not been demonstrated to be present in pediatric cancers. These factors make pediatric studies impossible or highly impractical to conduct and ^{177}Lu-PSMA-617 is very unlikely to provide benefit to pediatric patient population. Based on these considerations, on October 6, 2021, the FDA issued an Agreed initial Pediatric Study Plan (iPSP) granting a full waiver from the requirements of PREA.

11 Labeling Recommendations

The Applicant's Position:
As this is a new NDA, this section is not applicable.

The final USPI for TRADENAME reflects several changes from the version originally submitted by the Applicant. Notable changes and critical elements that were discussed with the Applicant during the NDA review include the following:

FDA's assessment:

Table 41. Summary of Significant Labeling Changes

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1. Indications and Usage	(b) (4)	FDA revised to: PLUVICTO is a radioligand therapeutic agent indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.
2. Dosage and Administration	(b) (4)	FDA revised to: Select patients for treatment using LOCAMETZ® or an approved PSMA-11 imaging agent based on PSMA expression in tumors. Recommended Dosage: Administer 7.4 GBq (200 mCi) every 6 weeks for up to 6

		doses. Dose interruption, reduction, or permanent discontinuation may be required due to adverse reactions.
2. Dosage and Administration	2.2. Patient selection: Identify patients for treatment by PSMA imaging.	FDA revised to the following: Select patients with previously treated mCRPC for treatment with PLUVICTO using LOCAMETZ or another approved PSMA-11 imaging agent based on PSMA expression in tumors. Additional selection criteria were used in the VISION study.
2. Dosage and Administration	2.4. Dose Modifications for Adverse Reactions	FDA added the new dose level after 20% dose reduction [i.e., 5.9 GBq (160 mCi)]. FDA added permanent discontinuation criteria for all ARs in the table. FDA removed (b) (4) (b) (4) FDA added "fatigue", "electrolyte or metabolic abnormalities (b) (4) (b) (4) (b) (4) and "other non-hematological

		toxicities" to the table. FDA removed (b) (4) (b) (4) FDA added dose interruption/reduction recommendations for grade 2 dry mouth.
2. Dosage and Administration	2.5 Preparation and Administration	FDA revised "slow intravenous push" to "within approximately 1 to 10 minutes" to specify a specific duration (in minutes) for clarity.
2. Dosage and Administration	2.6 Radiation Dosimetry ...	FDA removed (b) (4) (b) (4) from the table of estimated dosimetry.
5. Warnings and Precautions	5.2 Myelosuppression	FDA increased the incidence rates for myelosuppression ARs and added two deaths due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia in patients treated with PLUVICTO.
5. Warnings and Precautions	5.5 Infertility	FDA added the Warning and Precaution for infertility.
6. Adverse Reactions	6.1 Clinical Trials Experience ...	FDA added fatal adverse reactions, serious adverse reactions, and adverse reactions that led to dose interruption/reduction, and treatment discontinuation.

		FDA revised Table 3 and Table 4 to include the following: Table 3: Adverse Reactions (>5%) Occurring at a Higher Incidence in Patients with PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC Compared to BSoC Alone in VISION. Table 4: Select Laboratory Abnormalities (> 10%) That Worsened from Baseline in Patients With PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC (Between Arm Difference of ≥ 5% All Grades) in VISION.
8. Use in Specific Populations	8.1 Pregnancy ...	FDA revised to the following: The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm. There are no available data on PLUVICTO use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm.

8. Use in Specific Populations	8.5 Geriatric Use …	FDA removed (b) (4) [redacted] (b) (4) FDA added summary of efficacy and safety data in patients ≥75 years.
8. Use in Specific Populations	8.6 Renal Impairment …	FDA added the following: Exposure of lutetium Lu 177 vipivotide tetraxetan is expected to increase with the degree of renal impairment. …patients with mild or moderate renal impairment may be at greater risk of toxicity. Frequently monitor renal function and adverse reactions in patients with mild to moderate renal impairment.
12. Clinical Pharmacology	12.2. Pharmacodynamics (b) (4) [redacted]	FDA revised to: At the recommended dosage, PLUVICTO does not cause large mean increases (> 20 ms) in the QTc interval.
12. Clinical Pharmacology	12.3. Pharmacokinetics …	FDA revised to "The blood lutetium Lu 177 vipivotide tetraxetan area under the curve (AUC) is 52.3 ng.h/mL (31.4%) and the maximum

		blood concentration is 6.58 ng/mL (43.5%) at the approved recommended dosage". FDA added "Within 2.5 hours of administration, lutetium Lu 177 vipivotide tetraxetan distributes to gastrointestinal tract, liver, lungs, kidneys, heart wall, bone marrow, and salivary glands". FDA revised to "The lutetium Lu 177 vipivotide tetraxetan terminal elimination half-life is 41.6 hours (68.8%)". FDA revised the "Special populations" section to: "Exposure (AUC) of lutetium Lu 177 vipivotide tetraxetan increased with decreasing creatinine clearance (CLcr). The effect of baseline CLcr < 54 mL/min on lutetium Lu 177 vipivotide tetraxetan pharmacokinetics has not been studied."
13. Nonclinical Toxicology	13.1. Carcinogenesis, mutagenesis, impairment of fertility	FDA added "No animal studies were conducted to determine the effects of lutetium Lu 177 vipivotide tetraxetan on fertility." FDA removed (b) (4) (b) (4)

		information.
14. Clinical Studies		FDA revised the description of VISION and added the selection criteria based on 68Ga-PSMA-11 PET CT scan. FDA removed (b) (4) (b) (4) and added: "Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early drop out in the control arm." FDA removed (b) (4) (b) (4) FDA removed (b) (4) (b) (4) FDA removed (b) (4) (b) (4) FDA removed (b) (4) (b) (4) FDA removed (b) (4) d (b) (4) FDA removed (b) (4) (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS was required for this application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

BACKGROUND:

On February 16th, 2022 the FDA requested the Sponsor provide timeline proposals for two PMRs and one PMC with respect to the 177Lu-PSMA-617 original NDA 215833. A response was provided by the Applicanton February 22nd, 2022.

On March 2nd, 2022 the FDA provided additional comments on the PMRs and PMC and the timetables. A response was provided by the Applicant on March 8th.

PMR #1

Conduct an integrated safety analysis to further characterize the long term outcome of the known serious risk of myelosuppression, renal failure, xerostomia and xerophthalmia and their complications; the potential serious signals of secondary malignancies including myelodysplastic syndrome and acute myeloid leukemia (MDS/AML); and other serious adverse reactions in patients receiving lutetium (177Lu) vipivotide tetraxetan in the VISION study and its sub-study, Trial CAAA617C12301 (NCT04720157), Trial CAAA617B12302 (NCT04689828) and other clinical trials as appropriate. Capture data prospectively in amended case report forms to include incidence, grade, date of onset and resolution of the adverse reaction, predisposing factors and outcomes, date and quantity of red cell and platelet transfusion, use of growth factors for myelosuppression, subsequent antineoplastic therapies, radiation therapy, and hospital admissions. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first.

Milestones

Draft Protocol Submission (Analysis Plan):	09/2022
Final Protocol Submission (Analysis Plan):	03/2023
Interim Report Submission #1	09/2025
Interim Report Submission #2	09/2028
Trial Completion:	09/2033
Final Report Submission:	03/2034

Include the datasets with the final report submission.

FDA's comment: To fulfill PMR #1, the Applicant proposed to (b) (4)

(b) (4)

(b) (4)

PMR #2

Conduct a clinical trial to determine the kidney biodistribution, dosimetry, pharmacokinetics, and safety of lutetium (177Lu) vipivotide tetraxetan and assess the potential for higher drug exposure and the resultant risk of increased serious toxicities in patients with moderate and severe renal impairment. Assess long-term toxicities in these patients. Follow all patients until death, loss to follow-up, or for up to 10 years, whichever occurs first.

Milestones

Draft Protocol Submission:	12/2022
Final Protocol Submission:	03/2023
Trial Completion:	06/2026
Final Report Submission:	12/2026

FDA's comment: To fulfill PMR #2, the Applicant proposed (b) (4)

(b) (4)

(b) (4)

PMC #1

Conduct a clinical trial to evaluate the efficacy and safety of lutetium (177Lu) vipivotide tetraxetan in patients with advanced/metastatic prostate cancer who have at least one lesion with PSMA expression higher than that in normal liver parenchyma on PSMA-11 PET scan and at least one lesion with PSMA expression less than or equal to uptake in normal liver, with the following size criteria in short axis: size criteria in short axis: organs > 1 cm, lymph nodes > 2.5 cm, bones (soft tissue component) > 1 cm. Alternatively, add cohorts of these patients to ongoing trials. Include an analysis of these safety and efficacy data.

Milestones

Draft Protocol Submission:	09/2022
Final Protocol Submission:	03/2023
Trial Completion:	02/2026
Final Report Submission:	08/2026

FDA's comment: To fulfill PMC #1, the Applicant proposed to (b) (4)

(b) (4)

(b) (4)

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

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The FDA's References:

FDA's additional references:

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19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number)*: PSMA-617-01 (VISION)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified:		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 4		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): PSMA-617-02 (RESIST-PC)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:
No issues were identified upon FDA review.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not Applicable

The FDA's Assessment:
Refer to Pharmacology/Toxicology review.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

Pharmacometrics Review Summary
In general, the applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table **Error! Reference source not found.Error! Reference source not found.**. APPEARS THIS WAY ON ORIG NAL

Table 42. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	(b) (4)	Recommend deleting reference to (b) (4) (b) (4)
	Extrinsic factor	NA	NA
Derive exposure metrics for Exposure-response analyses	Cmax and AUC and quantification of radiation exposure		Derived by non-compartmental or population methods or acquired from organs.
Predict exposures at	NA		NA

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

alternative dosing regimen		

Population PK Analyses

Aims: 1) To characterize the overall radioactivity-blood PK of [177Lu]Lu-PSMA-617 and PK parameters (e.g. clearance, volume) with their variability in mCRPC patients; 2) To explore covariates (i.e. weight, BMI, age, baseline creatinine clearance) that may explain the inter-individual variability on PK parameters in this population; and 3) To predict individual PK (Bayes Estimates) and derive exposure metrics (i.e. AUCinf and Cmax) for E-R analyses.

Data: Radioactivity-blood PK, organ dosimetry and acute toxicity data during Cycle 1 from the PSMA-617-01 sub-study, which was conducted in a non-randomized cohort of 30 patients to provide a more complete assessment of the PK, dosimetry and some safety aspects of [177Lu]Lu-PSMA-617. The popPK dataset included 265 blood PK observations from 30 individuals after the first dose administration. Dosimetry assessments for each organ of interest (i.e. bone marrow, kidney, lacrimal glands and salivary glands) were available from 29 patients. Longitudinal laboratory data during Cycle 1 as well as any adverse events related to the organs at risk were collected for the 30 subjects. Summary of demographic variables and baseline characteristics is shown in Table .

Table 43. Summary of demographic variables and baseline characteristics.

	Continuous variables					
	Min	**1st quartile**	**Median**	**Mean**	**3rd quartile**	**Max**
Age (years)	52.0	61.5	67.0	66.7	72.8	80.0
Weight (kg)	63.8	78.5	88.8	89.9	97.8	143.0
BMI (kg/m^2)	18.3	24.8	28.4	28.6	31.8	38.8
	Min	**1st quartile**	**Median**	**Mean**	**3rd quartile**	**Max**
$CrCl_{BL}$ (mL/min)	54.0	85.6	98.0	106.6	132.6	201.0
	Categorical variables – number of patients (%)					
Race: White	30 (100%)					
Ethnicity:						
Not Hispanic or Latino	25 (83.3%)					
Hispanic or Latino	1 (3.3%)					
Not reported	4 (1.3%)					

$CrCl_{BL}$: baseline creatinine clearance; BMI: body mass index.

Source:Table 7-2 in the PopPK report.

Model Development: First, a base popPK model was developed including components of the structural model, random effect and residual error models that adequately characterized the

radioactivity-blood PK of decay-corrected [177Lu]Lu-PSMA-617. Next, a full model was constructed by incorporating covariate-parameter relationships with Pearson correlation coefficient ≥ 0.3 between post-hoc random effect and covariate. The investigated covariates of interest include age, weight, CrClBL and BMI at baseline. A three-compartment model with a delayed 0-order absorption and linear elimination adequately described the radioactivity-blood PK data. Baseline creatinine clearance (CrClBL) had a statistically significant impact on clearance (Cl), with a decrease of CrClBL by 40%, such as a decrease from 101.5 mL/min to 60.9 mL/min, leading to an average decrease of Cl by 21%. Baseline weight (WTBL) had a statistically significant impact on the central volume of distribution (V1), with a decrease of WTBL by 23%, such as a decrease from 88.5 kg to 68.1 kg, leading to an average decrease of V1 by 18%. The parameter estimates of the final model are presented in Table . The model was further assessed by diagnostic and performance plots (see Figure 1).

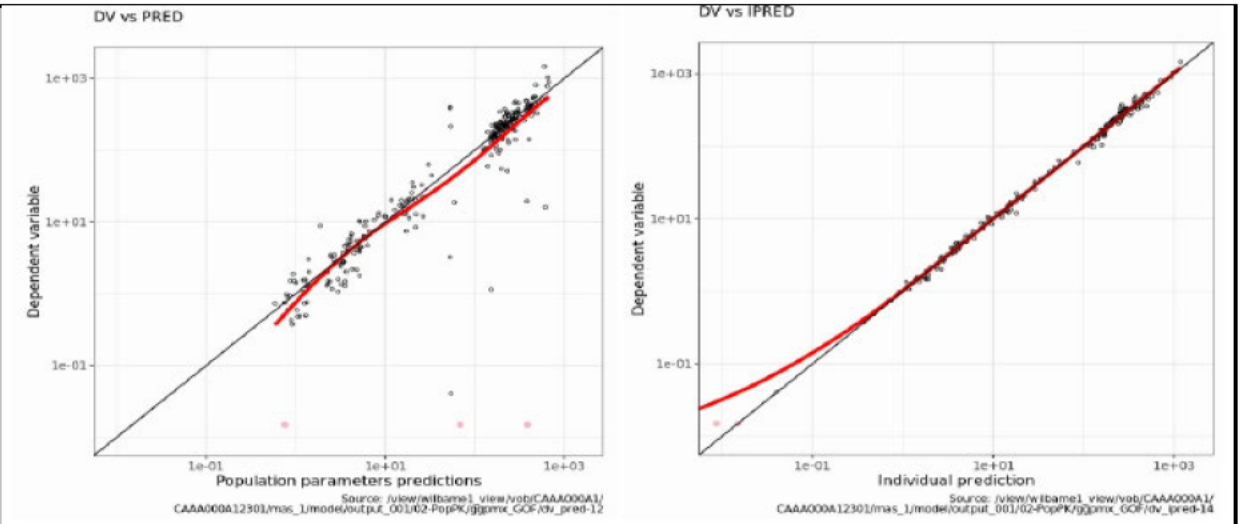
Table 44.Parameter Estimates from the Final PopPK Model.

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

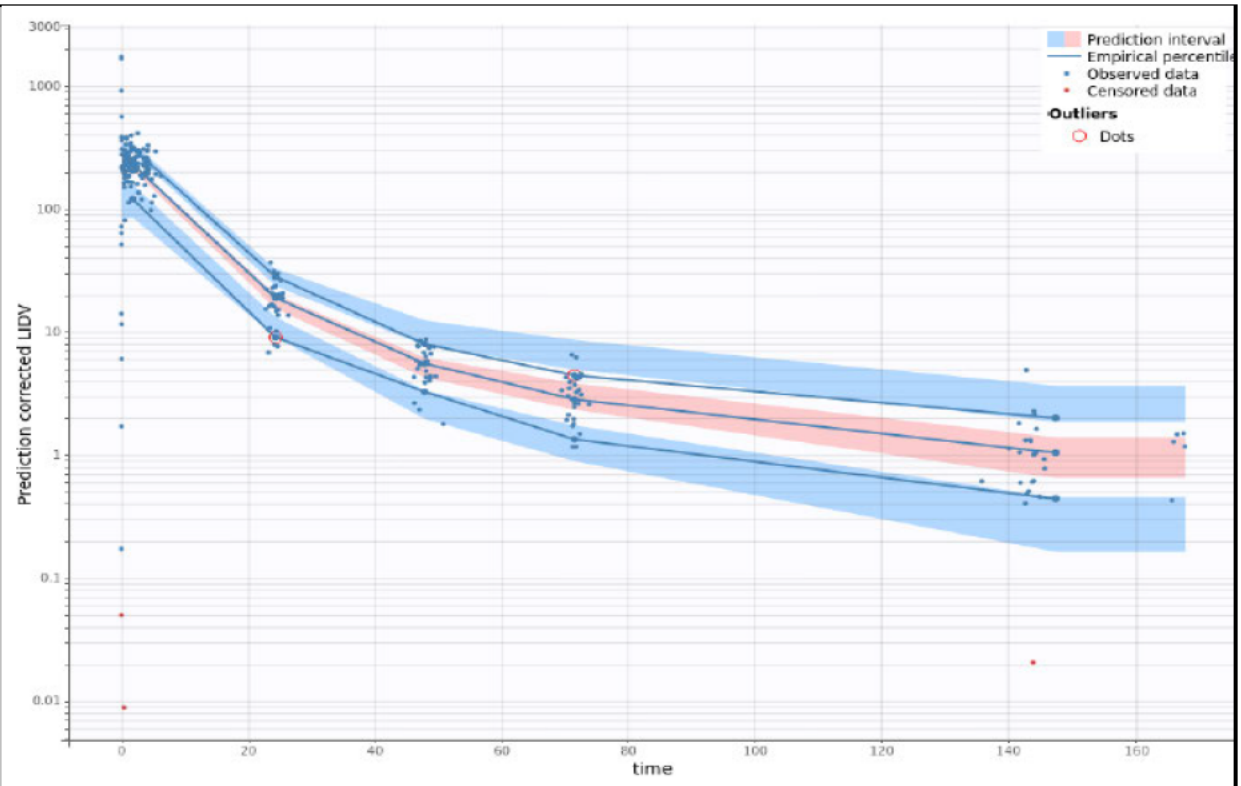
$CrCl_{BL}$: baseline creatinine clearance; CV: coefficient of variation; IIV: inter-individual variability; NA: not applicable; RSE: relative standard error; SD: standard deviation; SE: standard error; WT_{BL}: baseline weight; 0 FIX: fixed variability to 0.
CV (%) was calculated using $\sqrt{e^{SD^2}-1}\cdot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

Source: Table 7-6 in the PopPK report.

Figure 12. Plots for PopPK Model Evaluation.



Black dots are the concentrations above the LOQ and red dots the concentration below the LOQ. The black line is the identity line and the red curve a smooth line. The dependent variable is the concentration in kBq/mL.



The time corresponds to the time after start of infusion, in hours. LIDV corresponds to the concentration in kBq/mL. Solid lines display observed 10th, 50th, 90th percentiles. Blue/Pink regions show 90% prediction interval around the percentiles. Blue dots are the concentrations above the LOQ and red dots the simulated concentrations below the LOQ.

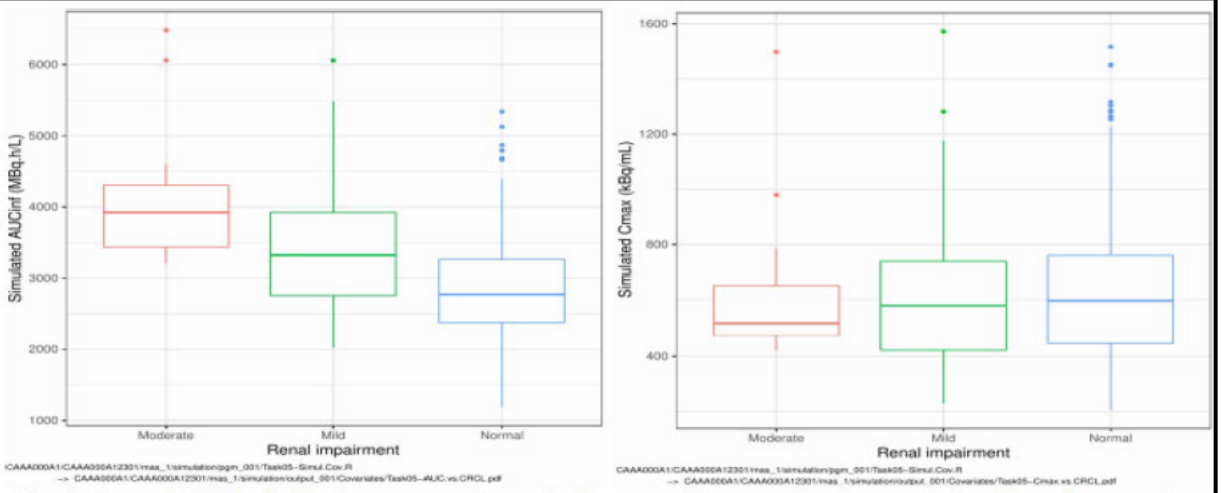
Source: Figures 7-11 and 7-13 in the PopPk report.

Simulations: Individual patients' data, including dosing information, WTBL and CrClBL values, were used to predict longitudinal concentrations during the first cycle and to derive Cmax and AUCinf for the 30 sub-study patients. The results as in

Figure 13 and Table showed a 42% and 20% increase in median of simulated AUCinf for moderate and mild renal impairment (based on CrClBL) respectively vs. for normal renal function. There was no significant effect of renal function on Cmax and of WTBL on Cmax.

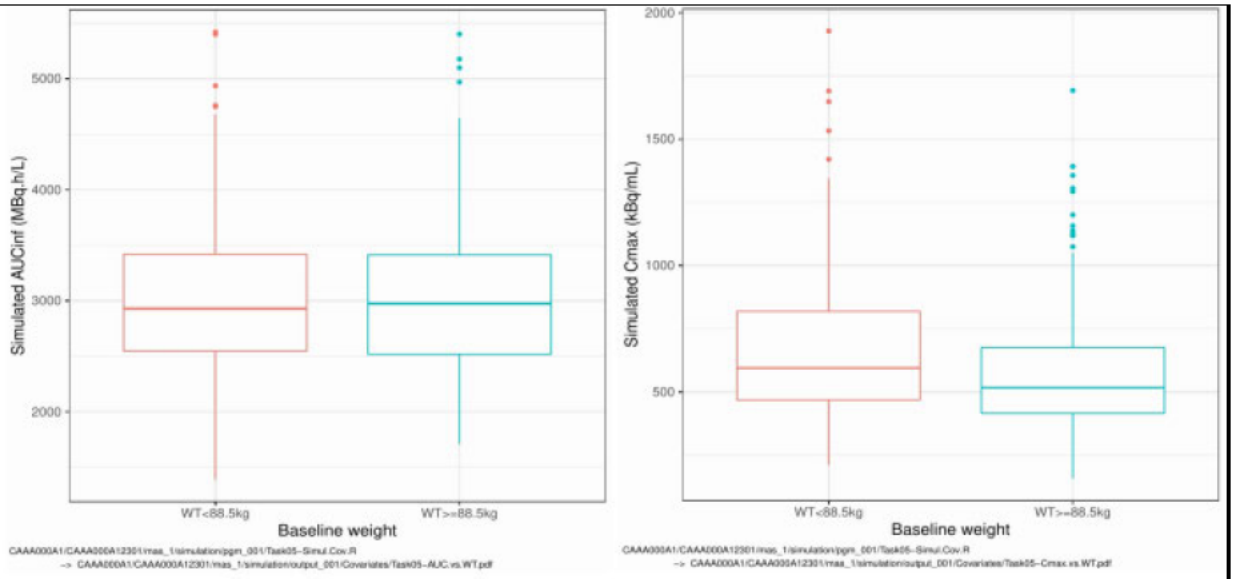
However, the simulation results should be interpreted with caution since in the popPK dataset there is only one patient with modetrate renal impairment and body weight range is narrow.

Figure 13 and Table 45. Summary of simulated AUCinf and Cmax by baseline renal impairment and baseline weight categories.



Simulations of 500 individuals were performed with covariates randomly sampled with replacement from the observed values. Only one individual had a moderate renal impairment ($CrCl_{BL}$=54mL/min). For each box plot, the top horizontal line is the 3rd quartile, the middle line is the median and the bottom line is the 1st quartile.

PK metrics	Simulated group	Min	1st Quartile	Median	3rd Quartile	Max
	Baseline renal impairment					
AUCinf (MBq.h/L)	Moderate	3202	3436	3924	4304	6482
	Mild	2019	2753	3323	3923	6057
	Normal	1192	2371	2767	3262	5337
Cmax (kBq/mL)	Moderate	420	476	519	651	1498
	Mild	228	422	578	739	1572
	Normal	206	447	597	760	1517



Simulations of 500 individuals were performed with covariates randomly sampled with replacement from the observed values. For each box plot, the top horizontal line is the 3rd quartile, the middle line is the median and the bottom line is the 1st quartile.

PK metrics	Simulated group	Min	1st Quartile	Median	3rd Quartile	Max
	Baseline weight					
AUCinf (MBq.h/L)	WT_{BL} < 88.5 kg	1391	2546	2930	3420	5420
	WT_{BL} ≥ 88.5 kg	1710	2517	2974	3412	5402
Cmax (kBq/mL)	WT_{BL} < 88.5 kg	211	469	595	820	1928
	WT_{BL} ≥ 88.5 kg	159	416	517	676	1693

Source: Figures7-14, 7-15 and Table 7-8 in the PopPK report.

Exposure-Response Analyses

Since Study PSMA-617-01 (main study) did not include PK or dosimetry, no exposure-response analysis with either efficacy or safety could be carried out. For the 30 patients in the PSMA-617-01 sub-study, where PK parameters were derived by either (non-)compartmental or populations methods and organ (but not tumor) dosimetry was acquired, both exposure metrics were used to explore the relationship between PK or organ radiation absorbed dose and acute toxicities related to the organ at risk as well on QT prolongation. Since the sub-study is still ongoing by the time of submission, only acute safety after the first dose of 177Lu-PSMA-617 was assessed.

The relationship between systemic exposure and absorbed dose in PSMA-expressing key organs were investigated. There was no consistent association between exposure metrics (i.e. injected activity, AUCinf, Cmax) and dosimetry in the organs at risk, namely kidney, bone marrow, salivary glands and lacrimal glands. Exposure-dosimetry analyses suggested that only

radioactivity-blood AUCinf was a statistically significant predictor of kidney dosimetry (p=0.005). However, the relationship between AUCinf and kidney dosimetry may not be a causal relationship as it is confounded by the inclusion of CrClBL as a covariate on Cl. Renal impairment (mild/moderate vs. normal) showed a trend toward higher kidney dosimetry values.

Results from the descriptive Exposure/Dosimetry-Toxicity analyses at Cycle 1 were: 1)Longitudinal laboratory profiles showed a decrease in leukocytes, neutrophils and platelets starting from 8 days after treatment administration; 2)Higher injected activity and higher kidney dosimetry tend to be associated with larger decrease from baseline in CrCl; and 3) No consistent trend was detected in the relationships between platelet count decrease, hematological adverse events and salivary gland toxicities with exposure metrics.

However, the exposure-response analyses are inconclusive due to data limitation.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Not Applicable. Additional safety analyses conducted by FDA are incorporated into Section 8.

NDA/BLA Multi-disciplinary Review and Evaluation (NDA 215833)
Pluvicto (177Lu-PSMA-617)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Wei Chen	OOD/DHOT	Section: 5	Select one: _X_ Authored _X_ Approved
	Signature: Wei Chen -S Digitally signed by Wei Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wei Chen -S, 0.9.2342.19200300.100.1.1=1300221221 Date: 2022.03.15 13:59:29 -04'00'			
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Section: 5	Select one: _X_ Authored _X_ Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2022.03.15 13:21:09 -04'00'			
Pharmacometrics Reviewer	Junshan Qiu	OCP/DPM	Section: 19.4	Select one: _X_ Authored ___ Approved
	Signature: Junshan Qiu -S Digitally signed by Junshan Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Junshan Qiu -S, 0.9.2342.19200300.100.1.1=2000348577 Date: 2022.03.15 13:24:16 -04'00'			
Pharmacometrics Team Leader	Jingyu (Jerry) Yu	OCP/DPM	Section: 19.4	Select one: _X_ Authored _X_ Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jingyu Yu -S, 0.9.2342.19200300.100.1.1=2000794699 Date: 2022.03.15 14:10:26 -04'00'			
Clinical Pharmacology Reviewer	Stacy Shord (signing on behalf of Sriram Subramaniam)	OCP/DCPI	Section: 6	Select one: _X_ Authored _X_ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2022.03.15 13:07:01 -04'00'			
Clinical Pharmacology Team Leader	Christy John	OCP/DCPI	Section: 6	Select one: _X_ Authored _X_ Approved
	Signature: Christy S. John -S Digitally signed by Christy S. John -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150005, cn=Christy S. John -S Date: 2022.03.16 22:06:30 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCPII	Section: 6	Select one: ___ Authored _X_ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2022.03.15 13:53:30 -04'00'			
Clinical Reviewer	Jaleh Fallah	OOD/DO1	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	Select one: _X_ Authored ___ Approved
	Signature: Jaleh Fallah -S Digitally signed by Jaleh Fallah -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jaleh Fallah -S, 0.9.2342.19200300.100.1.1=2003008737 Date: 2022.03.15 13:56:01 -04'00'			
Statistical Reviewer	Haley Gittleman	OD/DBV	Section: 8	Select one: _X_ Authored ___ Approved
	Signature: Haley R. Gittleman -S Digitally signed by Haley R. Gittleman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003042602, cn=Haley R. Gittleman -S Date: 2022.03.15 14:29:17 -04'00'			
Statistical Team Leader	Mallorie Fiero	OD/DBV	Section: 8	Select one: _X_ Authored _X_ Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2022.03.16 17:08:38 -04'00'			
Division Director (OB)	Shenghui Tang	OD/DBV	Section: 8	Select one: ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2022.03.17 12:20:41 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling (ADL)	William Pierce	OND/OCE	Sections: 11, Prescribing Information, Patient Information	**Select one:** _X_ Authored _X_ Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S Date: 2022.03.15 15:20:09 -04'00'			
Nonclinical Team Division Director (NME only)	John Leighton	OOD/DHOT	Section: 5	**Select one:** ___ Authored _X_ Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.03.15 15:50:49 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Sundeep Agrawal	OOD/DO1	Sections: All	**Select one:** _X_ Authored _X_ Approved
	Signature: Sundeep Agrawal -S Digitally signed by Sundeep Agrawal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001508741, cn=Sundeep Agrawal -S Date: 2022.03.16 00:49:52 -04'00'			
Deputy Division Director (Clinical)	Amna Ibrahim	OOD/DO1	Sections: All	**Select one:** __ Authored _X_ Approved
	Signature: Amna Ibrahim -S Digitally signed by Amna Ibrahim -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amna Ibrahim -S, 0.9.2342.19200300.100.1.1=1300150984 Date: 2022.03.17 14:16:32 -04'00'			
Supervisory Associate Director	Paul Kluetz	OND/OOD	Sections: All	**Select one:** __ Authored _X_ Approved
	Signature:			

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/s/

DUYEN M MACH
03/23/2022 01:06:31 PM

SUNDEEP AGRAWAL
03/23/2022 01:08:38 PM

PAUL G KLUETZ
03/23/2022 02:00:55 PM
I have reviewed and concur with the findings in the review document.