

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215841Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 23, 2022

CDTL: Anthony Fotenos, M.D., Ph.D.

Division Director: Libero Marzella, M.D., Ph.D.

SUBJECT: Addendum to Multidisciplinary Assessment Aid

APPLICATION/DRUG: NDA 215841 Locametz (gallium 68 (68Ga) gozetotide)

Following finalization of this review for Locametz, the Applicant agreed to additional changes to the Pluvicto PI as excerpted under Section 8.1.2 (“Study Results – VISION Trial”) of this review. In particular, (b) (4)

was removed,

(b) (4)

Finally, the following sentence was appended to the last excerpted paragraph beginning, “VISION demonstrated a statistically significant improvement in both major efficacy outcome measures of OS and rPFS by BICR with PLUVICTO plus BSoC compared to treatment with BSoC alone”: “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”. Note that these changes do not impact any review findings regarding Locametz.

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/s/

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NDA Multi-disciplinary Review and Evaluation

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.

Application Type	NDA
Application Number	215841
Priority or Standard	Standard
Submit Date	July 29, 2021
Received Date	July 29, 2021
PDUFA Goal Date	May 29, 2022
Division/Office	DIRM/OSM
Review Completion Date	2/22/2022
Established Name	⁶⁸ Ga-PSMA-11
(Proposed) Trade Name	Locametz
Pharmacologic Class	Radioactive diagnostic agent (for PET imaging)
Code Name	gallium (⁶⁸ Ga) gozetotide
Applicant	Advanced Accelerator Applications USA, Inc., a Novartis Company
Formulation	Kit for Injection
Dosing Regimen	(b) (4) 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi).
Applicant Proposed Indications/Populations	After radiolabeling with gallium-68, is indicated 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 prostate-specific antigen (PSA) level. • for (b) (4) of patients with metastatic prostate cancer, for whom PSMA-targeted therapy is indicated.
Recommendation on Regulatory Action	Standard Approval
Recommended Indications/Populations	LOCAMETZ, after radiolabeling with gallium-68, is a radioactive diagnostic agent indicated 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 prostate-specific antigen (PSA) level. • for selection of patients with metastatic prostate cancer, for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated

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Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

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Multi-disciplinary Review and Evaluation
 NDA 215841, Locametz/gallium Ga 68 gozetotide

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BCR	Biochemical recurrence
BICR	blinded independent central review
BLA	biologics license application
BRF	Benefit Risk Framework
BSC/BSoc	best Supportive/Best Standard of Care
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GOZ	gallium Ga 68 gozetotide, Ga68-PSMA-11, etc.
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	intent to treat
MBq	Megabequerel
mCi	Millicurie
mCRPC	metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
NPV	Negative predictive value
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

Multi-disciplinary Review and Evaluation
NDA 215841, Locametz/gallium Ga 68 gozetotide

PC	prostate cancer
PD	pharmacodynamics
PET	Positron emission tomography
PI	prescribing information
PK	pharmacokinetics
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SUV _{max}	Maximum standardized uptake value
TEAE	treatment emergent adverse event
UCLA	University of California Los Angeles
UCSF	University of California San Francisco
VIP	lutetium Lu 177 vipivotide tetraxetan, Lu177-PSMA-617, etc.
UCSF	University of California San Francisco

1 Executive Summary

1.1. Product Introduction

The Applicant, Advanced Accelerator Applications (AAA), is seeking U.S. Food and Drug Administration (FDA) approval to market Locametz in the United States per authority granted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The drug substance in Locametz is gallium Ga 68 gozetotide (GOZ). GOZ is also known as Ga68-PSMA-11. GOZ is a peptide-based, positron-emitting radiopharmaceutical that binds to prostate-specific membrane antigen (PSMA), a protein overexpressed in prostate cancer (PC). After Locametz is prepared and administered intravenously, GOZ concentrates at binding sites containing PC. From these and other sites of off-target binding or biodistribution, gallium 68 decay leads to release of positrons and emission of dual 511 keV photons that can be imaged.

Locametz provides GOZ in a kit formulation. Formulated as a finished radiolabeled injection, GOZ has been approved and listed in FDA's Orange Book of approved drug products (LD). The LD was approved for detection of PC lesions (disease detection) in patients with primary and early metastatic PC. This new drug application (NDA) relies on FDA's findings for the LD for assessment of the Applicant's proposed disease detection indications.

For patients with advanced metastatic castration resistant PC (mCRPC), the Applicant is also seeking approval of a new indication type in this NDA: patient selection. The selection is for eligibility to receive lutetium Lu 177 vipivotide tetraxetan (VIP) therapy. In parallel with this NDA, the Applicant submitted another NDA to market VIP injection under the tradename Pluvicto. Pluvicto (VIP) is a new molecular entity (NME), and Locametz (GOZ) is a new formulation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided in vitro and clinical pharmacology data to support a scientific bridge between Locametz and the LD. Accordingly, FDA's findings for the LD provide substantial evidence that Locametz is effective for the disease detection indications proposed.

In addition, evidence of effectiveness for the Applicant's new patient selection indication derives from a randomized, multicenter, open-label trial in patients with advanced mCRPC (VISION; 1218 participants). Substantial evidence from the VISION trial and confirmatory evidence from additional VISION studies together showed that VIP treatment in GOZ-selected patients improved patient outcomes, including OS; that Fleiss' kappa for readers to select patients was 0.6 (95% confidence interval [95%CI] 0.5 to 0.7); that outcomes appeared to be improved in the subgroup of VIP-treated patients with relatively more versus less GOZ uptake on baseline imaging; and that GOZ and VIP share overlap in biodistribution. The review team thus concluded that Locametz is effective to select patients with metastatic PC, for whom VIP therapy is indicated.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Prostate cancer (PC) is the second leading cause of cancer-related death among men in the United States. In addition to the mortality burden, PC results in a significant negative impact on quality of life. There is an urgent need for more effective treatments and management strategies to improve outcomes for patients with PC. Effective treatment of PC is dependent upon accurate and reliable detection and assessment of the extent of disease. However, diagnostic challenges persist despite recent imaging advances, such as multiparametric MRI and PET drugs approved for prostate cancer, such as 11C-choline and 18F-fluciclovine.

Gallium Ga 68 gozetotide (GOZ), which is also known as Ga68-PSMA-11, is a positron emitting radiopharmaceutical that targets prostate-specific membrane antigen (PSMA), a cell surface protein mainly expressed on malignant cells. The Applicant seeks approval for a kit for the preparation of GOZ for intravenous administration, based on FDA's prior approval of GOZ injection, plus the Applicant-conducted VISION trial and VISION studies. The listed drug (LD), GOZ injection, has been approved under NDA 212643.

In the VISION trial, subjects with metastatic castration resistant prostate cancer underwent GOZ PET imaging for evaluation per pre-specified interpretation criteria for patient selection. Only selection-positive subjects were eligible for randomization and receipt of lutetium Lu 177 vipivotide tetraxetan (VIP). The VISION trial met both of its alternate primary efficacy objectives with rPFS and OS improved in subjects randomized to the VIP plus Best Standard of Care / Best Supportive Care (BSC/BSoC) arm over the BSC/BSoC arm. The VISION trial thus demonstrated improved clinical outcomes in patients treated with VIP after use of GOZ for patient selection. In particular, of the 995 subjects eligible for randomization, 869 (87%) were selected. Additional VISION studies together showed that Fleiss' kappa for readers to select patients was 0.6 (95%CI 0.5 to 0.7); that outcomes appeared to be improved in the subgroup of VIP-treated patients with relatively more versus less GOZ uptake on baseline imaging; and that GOZ and VIP share overlap in biodistribution.

For safety evaluation, the available safety study dataset was supplemented with adverse event data from 1003 patients with mCRPC who received GOZ. Treatment emergent adverse events were uncommon. Radiation effective dose from GOZ is typical of PET oncology imaging and estimated to impart minimal additional stochastic risk in this patient population. Risk of misdiagnosis, including a warning and precaution specific to finding variability in patient selection, are addressed through labeling.

In summary, the benefit of Locametz in the indicated patient populations outweighs the acceptably low risks. Approval of this application is warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• PC is the most common cancer in American men and the second leading cause of cancer-related death in this population. • The course of PC varies widely. While many men will have slow growing cancer that needs no treatment, others will have aggressive disease that leads to pain, debilitation, and death. • The pelvic lymph nodes are typical sites of local/regional spread. • Proper management of PC involves assessment of the risk of aggressive disease as well as evaluation of the location and extent of disease. • Effective treatment of PC is dependent upon accurate and reliable detection and assessment of the extent of disease and patient selection. • The tumor target, PSMA, has been confirmed as a biological target for diagnostic imaging and therapy in PC.	PC is a serious condition that causes substantial morbidity and mortality. Imaging of disease can have important impact on patient management. The differential expression of PSMA from tumor to non-tumor tissue supports targeted strategies in PC involving both disease localization using nuclear medicine imaging as well as treatment with radioligand therapeutic intervention.
<u>Current Treatment Options</u>	• Many imaging techniques have been applied to PC, including ultrasound, computed tomography (CT), MRI, bone imaging using Tc 99m medronate or F 18 fluoride, In 111 capromab pentetide SPECT, and PET using C 11 -choline, F 18 fluciclovine, GOZ, or F 18 piflufolastat. The technique used varies depending on what information is needed. • For patients with newly diagnosed PC who are at intermediate or higher risk, treatment choice is influenced by whether cancer has spread to regional lymph nodes and more distant sites. Standard-of-care imaging has traditionally relied on Tc 99m medronate bone scan along with CT or MRI of the abdomen and pelvis to detect such metastases. The diagnostic performance of these techniques is moderate. Recurrent PC after prostatectomy has been estimated to occur in up to 30% of men who had no evidence of metastatic disease on initial conventional imaging. While therapeutic methods may be a factor, this recurrence rate suggests that disease outside	Despite the availability of many different techniques for imaging prostate cancer, there is an unmet need for better diagnostic performance Traditional standard -of-care imaging in most scenarios is based largely on anatomic modalities such as CT and MRI, which are best at finding large lesions. Functional bone imaging tends to be either insensitive at lower, clinically relevant PSA levels in the case of Tc 99m medronate or limited by low specificity in the case of F18 fluoride. C 11 choline and F 18 fluciclovine are PET drugs approved specifically for imaging of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the prostate gland is missed by traditional imaging technique in a number of cases. - PC recurrence is usually first recognized due to an increase in serum PSA level. Bone scan and CT or MRI are traditionally used to locate recurrent disease, because this information might guide optimal therapy. PET performed with C 11 choline, F 18 fluciclovine, GOZ, and F 18 piflufolastat might also be used as they are specifically approved for prostate cancer imaging in the setting of biochemical recurrence. There is a desire for higher detection rate when the PSA level is low. - Once patients reach the metastatic castration-resistant prostate cancer (mCRPC) stage, their expected overall survival is low, and current treatments for mCRPC provide a limited 5-year survival rate.	prostate cancer in patients with biochemical recurrence. Lesion detection rates with these agents are limited at the low PSA levels of early recurrence. GOZ injection and F 18 piflufolastat are PSMA-specific PET drugs recently approved for use in the initial therapy and biochemical recurrence settings. There is an urgent need for more effective treatments and management strategies to improve outcomes for patients with PC. Effective treatment of PC is dependent upon accurate and reliable patient selection.
<u>Benefit</u>	- Relied upon findings establish that GOZ is effective for detecting PC lesions. - There are pharmacological differences between the Applicant's kit product and the LD. - Sources of bridging information between the Applicant's kit and the RLD included in vitro and clinical pharmacology data. - Substantial evidence from the VISION trial and confirmatory evidence from additional VISION studies together showed that VIP treatment in GOZ-selected patients improved patient outcomes, including OS; that Fleiss' kappa for readers to select patients was 0.6 (95%CI 0.5 to 0.7); that outcomes appeared to be improved in the subgroup of VIP-treated patients with relatively more versus less GOZ uptake on baseline imaging; and that GOZ and VIP share overlap in biodistribution. Uncertainties remain concerning patient selection variability and optimization.	A scientific bridge between the Applicant's kit and the LD was established. Locametz, 111 MBq to 259 MBq (3 mCi to 7 mCi), is effective for PET imaging of PSMA-positive lesions in men with PC with suspected metastasis who are candidates for initial definitive therapy; with suspected recurrence based on elevated serum PSA level; and for selection of patients with metastatic PC, for whom VIP PSMA-directed therapy is indicated. Agreed labeling and postmarketing studies address remaining uncertainties.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Risk and Risk Management</u>	• Relied upon findings establish that GOZ is safe in patients earlier in the course of PC, including the periods of initial definitive therapy and PSA recurrence. • No new safety signals were identified in the Applicant conducted trial of patients with advanced mCRPC.	The radiation effective dose of GOZ is typical of oncologic PET imaging. Use of Locametz as prescribed is safe.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
		☐ 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	No patient experience data was submitted in this application and none was needed.		

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Prostate cancer is the second leading cause of cancer-related death among men in the US (Siegel et al. 2020) and the third leading cause of cancer-related death in Europe (Malvezzi et al. 2019). In addition to the mortality burden, prostate cancer results in a significant negative impact on quality of life (Diels et al. 2015; Lloyd et al. 2015).

Once patients reach the metastatic castration-resistant prostate cancer (mCRPC) stage, their expected overall survival is low (Smith et al. 2016). Current treatments for mCRPC provide a limited 5-year survival rate (Moreira et al. 2017; Boettcher et al. 2019). Thus, there is an urgent need for more effective treatments and management strategies to improve outcomes for patients with PC. Effective treatment of PC is dependent upon accurate and reliable detection and assessment of the extent of disease.

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

Additionally, PSMA overexpression is correlated with advanced, high-grade, metastatic, castration-resistant prostate cancer (Wright et al. 1995; Silver et al. 1997; Bostwick et al. 1998; Murphy et al. 1998; Sweat et al. 1998; Ross et al. 2003; Chang 2004; Queisser et al. 2015). The differential expression of PSMA from tumor to non-tumor tissue supports targeted strategies in prostate cancer involving both disease localization using nuclear medicine imaging as well as treatment with radioligand therapeutic intervention.

Expression of PSMA is an independent predictor of poor prognosis (Chang 2004; Hupe et al. 2018), with significantly shorter survival and a higher risk of disease recurrence reported in patients with high levels of PSMA expression (Ross et al. 2003; Cimadamore et al. 2018; Hupe et al. 2018; Nagaya et al. 2020).

The FDA's Assessment:

The review team agrees that patients with PC have unmet medical needs and that PSMA is a rational molecular target for development of new radiopharmaceuticals. For additional analysis of PC pertinent to disease detection (i.e., earlier in the course of disease during periods of initial definitive or suspected recurrence therapy), see Section 2 of FDA's Multi-disciplinary Review and Evaluation for other approved PSMA imaging products. For additional analysis of PC pertinent to the Applicant's proposed patient selection indication (i.e., late in the course of

disease during the period of metastatic castration-resistant prostate cancer [mCRPC] following 2 to 3 lines of therapy), see Section 2 of FDA's Multi-disciplinary Review and Evaluation for Pluvicto.

Regarding the Applicant's position that PSMA expression is several hundred-fold lower in some normal tissues, the reader is cautioned that ratios derived from in vitro data may not translate directly to imaging or dosimetry metrics of clinical interest.

Regarding the Applicant's position that PSMA is an independent predictor of poor prognosis, recently published data provide additional support (Vlachostergios et al. 2021). Patients with high PSMA expression had shorter overall survival (OS) compared to those with low expression (16 vs 23 months). It thus appears that high PSMA expression generally portends a poor prognosis even late in the history of PC, in patients with mCRPC treated with standard systemic therapies. Caution against over-extrapolation to all patients is warranted, however, since neuroendocrine lesions that arise from adenocarcinoma in end-stage disease may have low or absent PSMA expression.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Diagnostic tools for prostate cancer include PSA testing, digital rectal palpation, transrectal ultrasound, prostate biopsy, and histopathologic examination (Schwarzenböck et al. 2012; Prasad et al. 2016; Smith et al. 2016). Additionally, further imaging techniques such as MRI, bone scintigraphy, CT, and [¹⁸F]Fluorodeoxyglucose, [¹⁸F]Choline, [¹¹C]Choline and the more recently approved [¹⁸F]fluciclovine (Nanni et al. 2016; Odewole et al. 2016) PET/CT are used for staging primary prostate cancer and restaging BCR (Schwarzenböck et al. 2012). CT, MRI and bone scan are the standard of care imaging procedures for measuring tumors at baseline and lesions selected for response assessment as per RECIST 1.1 (Eisenhauer et al. 2009). However, none of these imaging modalities identify PSMA-expressing tumors.

PSMA-expressing lesions in patients can be identified by histology and immunohistochemistry staining of biopsied samples, but these methods are invasive and subject to sampling bias as it is not possible to biopsy or dissect all lesions by surgery. By contrast, PSMA-targeted PET enables detection of PSMA-expressing tissue throughout the body at once, in a non-invasive manner. PSMA-targeted PET imaging offers the potential to both stage patients and provide insight into tumor biology, by detecting PSMA-expressing lesions.

GOZ adds diagnostic value to the treatment landscape by identifying patients who stand to benefit from targeted therapy or for whom assessment of the presence, extent, or location of disease will help determine the optimal treatment approach (Hofman et al. 2018; Hofman et al. 2021). A number of studies revealed higher sensitivity, specificity, and accuracy with GOZ PET compared to morphological imaging (CT and MRI) in the identification and staging of lymph node metastases, both on patient-based and template-based analyses. Additionally, the underlying mechanism of GOZ PET in detecting PSMA-expressing prostate cancer tumors, i.e. specific binding to PSMA, is universal across prostate cancer disease stages.

Clinical use of GOZ has been under compassionate use/expanded access laws or other local regulations, or more traditional investigative compound regulatory pathways such as clinical trials. Compound use as well as safety data collection has been managed by individual

investigators, partially coordinated by medical societies such as the Society of Nuclear Medicine and Medical Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM). GOZ use as a patient selection tool for PSMA-targeted therapy is in ongoing clinical trials.

The FDA recently granted UCLA and UCSF approvals for manufacture and use of GOZ Injection (Gallium 2020a; Gallium 2020b), a radioactive diagnostic agent indicated for positron emission tomography (PET) of PSMA positive lesions in men with prostate cancer. The FDA also recently approved 18F-DCFPyL (piflufolastat F 18) (PYLARIFY 2021), which is also a radioactive diagnostic agent indicated for PET of PSMA positive lesions in men with prostate cancer.

Published clinical imaging guidelines, as well as 10 years of documented use have demonstrated the relevance of GOZ PET in imaging of prostate cancer with increased PSMA expression. Consensus on the use of GOZ PET as an imaging tool, as well as the interpretation and reporting of its scans, have been outlined in several guidelines, which include the E-PSMA standardized reporting guidelines (Ceci et al. 2019), the European Association of Urology (EAU) guidelines on PC (EAU 2019; Cornford et al. 2021; EAU 2021), and the Joint EANM and SNMMI guideline (Fendler et al. 2017).

The FDA's Assessment:

The review team agrees that there are multiple approved options for detecting PSMA-positive lesions in men with PC prior to initial definitive therapy or with suspected recurrence based on elevated PSA. These include GOZ Injection, Pylarify (F18-piflufolastat), and Illuccix (kit for preparation of GOZ).

In this NDA for Locametz, in addition to approved disease detection indications, the Applicant is seeking approval of a new patient management indication: selection of patients with metastatic prostate cancer, for whom VIP therapy is indicated. No imaging agent (drug or biological product) has ever been approved to select patients for therapy. Tightly coupled therapeutic and diagnostic (“theranostic”) radiopharmaceutical indications apply, in general, to clinical contexts in which the distinction between potential imaging results is intended to guide decisions at the patient level *directly* about a particular therapeutic product (or narrowly defined group of products; here, for example, treating vs. not treating with VIP). Theranostic indications may be juxtaposed to the more common stand-alone variety. Stand-alone indications for imaging agents are intended primarily to provide reliable information about a patient’s anatomy, function, or disease. With respect to therapeutic decision-making, for stand-alone indications, clinical value is *indirect* or secondary to the primary value of information provided about the patient through product use. Detecting PSMA-positive lesions in men with PC prior to initial definitive therapy or with suspected recurrence is a stand-alone indication type.

Notably, the intended distinction between dichotomous results may differ for the same product under different indications. For disease detection, for example, the distinction between “Locametz positive” and “Locametz negative” is intended to distinguish whether a lesion in question is PSMA-positive PC versus benign or PSMA-negative PC. For patient selection, in contrast, the distinction between “Locametz positive” and “Locametz negative” is intended to distinguish whether the patient in question should receive VIP therapy, if otherwise eligible, or not. For additional information on patient management indications, refer to FDA’s Guidance for Industry titled, “Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies.” For additional information on VIP

co--development in parallel, including the Applicant’s synchronized submission of NDA 215833, see FDA’s Multi-disciplinary Review and Evaluation for Pluvicto.

In summary, there are currently no imaging options to compete with Locametz that have been approved for patient selection or any other theranostic radiopharmaceutical indication.

Table 1 provides an overview of the available stand-alone imaging options for patients with PC. The table has been updated from the summary developed under NDA 214032 and includes options not specifically approved for PC imaging, since labeled indications for imaging agents may be more narrowly linked to clinical evidence compared to their use in practice. Note that the NDA under review lacks evidence of comparative effectiveness based on adequate and well controlled head-to-head investigations. The reader is thus cautioned against drawing inferences from comparisons across rows (i.e., between studies) in the table. In addition, the review team disclaims the Applicant’s position in this section regarding comparative effectiveness.

Table 1. Imaging Prostate Cancer

Technique	Use in Practice	Performance Estimates	Comments
Ultrasound	Diagnosis (guide biopsy) restaging	Detection of prostate bed recurrence after RP: Sensitivity 76% Specificity 67%	Limited to prostate and prostate bed
CT	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 57% Specificity 68%	Poor performance for lesions contained within the prostate
MRI	Diagnosis (guide biopsy) Initial staging Restaging Active surveillance	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 59% Specificity 79% (using DWI)	Current best choice for imaging prostate gland
Tc 99m medronate	Initial staging Restaging Therapy monitoring	Detection of spinal metastases: Sensitivity 51% Specificity 82%	Limited to bone imaging Usually negative if PSA <10 ng/mL
F 18 sodium fluoride	Initial staging Restaging	Detection of spinal metastases: Sensitivity 93% Specificity 54%	Limited to bone imaging NCCN recommends second line use behind 99mTc-medronate due to lower specificity
In 111 capromab pendetide	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 63% Specificity 67% Identifying disease after BCR: PPV 50%	Approved for SPECT imaging of prostate cancer prior to definitive therapy and in the BCR setting Withdrawn from market by BLA holder
C 11 choline	Restaging	Identifying disease after BCR: PPV 82%	Approved for PET imaging of prostate

Technique	Use in Practice	Performance Estimates	Comments
			cancer only in the BCR setting Labeling indicates performance may be more reliable if PSA >2 ng/mL
F 18 fluciclovine	Restaging	Identifying disease after BCR: PPV 76% Detection rate 60% (for PSA ≤1.78 ng/mL) Detection rate 96% (for PSA >1.78 ng/mL)	Approved for PET imaging prostate cancer only in the BCR setting
Ga 68 gozetotide (GOZ)	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 47% Specificity 90% Identifying disease after BCR: PPV 91%	PSMA-targeted
F 18 piflufolastat	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 28-39% Specificity 95-98% Identifying disease after BCR: PPV 85-87%	PSMA-targeted

Source: Multi-disciplinary Review and Evaluation for NDA 214032.

Abbreviations: BCR, biochemical recurrence; BLA, biologics license application; CT, computed tomography; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; SPECT, single photon emission computed tomography

Table 2 provides a summary of preliminary investigation of GOZ for patient selection from literature sources.

Table 2. Preliminary Investigation of GOZ for Patient Selection

Study	Patient Selection	Therapy	Imaging Eligibility Criteria	Estimates
(Hofman et al. 2018) (LuPSMA trial); no randomized control arm	GOZ and FDG	VIP	Any one lesion: >1.5×SUV _{max} liver; All lesions: no FDG discordance	Subjects imaged: 43 Subjects treated: 30 Ineligibility rate: 16% Reader agreement: N/A
(Hofman et al. 2021) (TheraP trial); no randomized control arm	GOZ and FDG	VIP	Any one lesion: SUV _{max} ≥ 20; All measurable (≥10mm) lesions: SUV _{max} > 10; All lesions: no FDG discordance	Subjects imaged: 291 Subjects treated: 200 Ineligibility rate: 27% Reader agreement: N/A

Study	Patient Selection	Therapy	Imaging Eligibility Criteria	Estimates
(Yadav et al. 2021); no randomized control arm	GOZ	VIP	Soft tissue > liver; Skeletal > vertebra	Subject screened: 135 Subject treated: 121 Ineligibility rate: 4% Reader agreement: N/A

Source: Reviewer analysis of cited literature.
Abbreviations: FDG, F18-fludeoxyglucose; GOZ, Ga68-gozetotide; VIP, Lu177-vipivotide tetraxetan

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

In this document, the radiolabeled compound (company research code: AAA517) is referred to as GOZ, and the therapeutic agent is referred to as VIP.

Approval of GOZ Injection has been granted to the University of California Los Angeles (UCLA) and University of California San Francisco (UCSF) based on their New Drug Applications on 1-Dec-2020 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 prostate-specific antigen (PSA) level.*

Results from Study PSMA-617-01 (VISION) and the PSMA-617-01 Reviewer Variability analysis from Study PMSA-617-01, combined with FDA's assessment of safety and effectiveness of NDAs 212642 and 212643, were used.

The FDA's Assessment:

The review team agrees that FDA's first PSMA imaging agent approval was for use of GOZ Injection for disease detection under NDAs 212642 and 212643. The review team also agrees that FDA's findings for the listed drug (LD) under 212642 may be relied upon for 505(b)(2) review of Locametz (the Applicant's new kit formulation), provided reliance on the LD is limited to the approved disease detection indications, bridging is adequate, and exclusivity blocks do not apply. A relevant precedent action along the lines of the 505(b)(2) prong of the Applicant's approach to this NDA was demonstrated on 17-Dec-2021, under NDA 214032, when FDA approved Illuccix, the first approved kit formulation for preparation of GOZ. Illuccix was approved under the 505(b)(2) pathway, relying on FDA's findings for the same LD and disease detection indications as proposed by the Applicant in this NDA.

For additional background on the prong of the Applicant's approach reliant on new safety and efficacy data, see Section 2.2 for introduction to the theranostic concept and Section 3.2 for relevant submission activity.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of the key interactions with the FDA regarding the development of ⁶⁸Ga-PSMA-11 is provided in Table 3.

Table 3. Key FDA Interactions

Date	Purpose of Key Interactions
19-Dec-2018	Type B EOP2 Meeting to discuss clinical and non-clinical development plans.
04-Jun-2019	Type B WRO provided FDA feedback on draft charters for Reader Variability and Quantitative Analysis studies.
24-Mar-2020	Type C Pre-NDA Meeting to align on Module 2, 3 and 5 content and dataset expectations for NDA submission.
21-Jul-2020	Agreed iPSP Agreement received for localization of PSMA-expressing metastatic prostate cancer in adult patients.
13-Jan-2021	Proprietary name request for Locametz conditionally accepted.
02-Jun-2021	Type B Pre-NDA Meeting to obtain agreement on the proposed submission package for the NDA.

Source: NDA215841\0000\m1\us\fdareponse-multidisciplinary-assessment-aid.docx

Abbreviations: EOP2, End-of-Phase 2; NDA, New Drug Application; PSMA, prostate-specific membrane antigen; WRO, written responses only

The FDA's Assessment:

The review team agrees that on the multiple occasions specified in Table 3, FDA provided formal responses to the Applicant's questions submitted as sponsor of IND 133925. The questions mainly focused on strategy for efficient co-development in parallel under Oncology IND 133661 for VIP (where the VISION trial protocol was developed) and under DIRM IND 133925 for GOZ (where VISION imaging acquisition, analysis, and interpretation protocols or sub-protocols, charters, manuals, etc. were developed for the indication of patient selection). In particular:

For the meeting on December 19, 2018, FDA recommended that the Applicant gather evidence to support GOZ indications that may be directly related to VIP therapy.

For the WRO meeting granted on June 4, 2019, FDA agreed that substantial evidence established by the VISION trial plus confirmatory evidence from VISION studies could be sufficient for review of a 505(b)(2) NDA for GOZ for patient selection.

For the pre-NDA meeting on March 24, 2020, FDA recommended that the Applicant refocus their plans for 505(b)(2) submission to rely on an appropriate LD for established disease detection indications and on results of the VISION trial and sub-studies for the new patient selection indication.

For the meeting June 02, 2021, FDA agreed that top-line data appeared sufficient from DIRM's perspective to file parallel NDA submissions under DIRM NDA 215841 for Locametz and DOI NDA 215833 for Pluvicto.

The Applicant's original submission to both NDAs was synchronized on July 29, 2021.

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

4.1. Office of Scientific Investigations (OSI)

Refer to FDA’s Multi-disciplinary Review and Evaluation for Pluvicto for summary of inspection findings that VISION trial conduct was in accordance with Good Clinical Practice (GCP).

4.2. Product Quality

Refer to OPQ Review and Evaluation recommending approval.

4.3. Clinical Microbiology

Refer to OPQ Review and Evaluation recommending approval.

4.4. Devices and Companion Diagnostic Issues

Refer to FDA’s Multi-disciplinary Review and Evaluation for Pluvicto, indicated as follows:

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.

In addition, the FDA and Applicant agreed to the following language under Pluvicto labeling Section 2.1 (“Patient Selection”):

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 [see Clinical Studies (14)].

Refer to the prescribing information for the PSMA imaging agent.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment

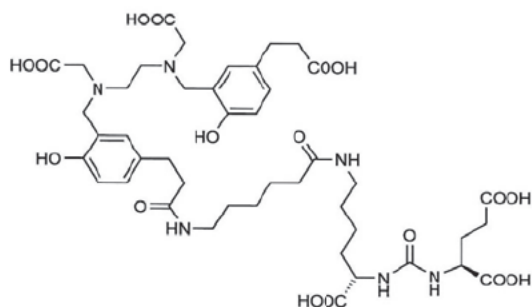
This NDA should be approved from a nonclinical perspective.

The submission supports the marketing authorization for the kit for the radiopharmaceutical preparation GOZ (Locametz) by the 505(b)(2) regulatory pathway. GOZ is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA)-positive lesions by in men with prostate cancer. The Applicant conducted nonclinical studies to support the application as well as a bridging study to demonstrate comparability between the Applicant's kit and GOZ approved under NDA 212642 and NDA 212643. The NDA is also supported by published nonclinical literature on the safety and activity of GOZ and available clinical experience for the listed drug (LD).

Pharmacology

GOZ is a PSMA-targeted radioactive diagnostic imaging agent for the PET identification of PSMA-positive lesions. GOZ is composed of a PSMA-targeting ligand, Glu-urea-Lys(Ahx), conjugated, via the acyclic radiometal chelator N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'-diacetic acid (HBED-CC), to the radioisotope ⁶⁸Ga (Eder et al. 2012). The binding of a high affinity ligand (GOZ) to cell surface PSMA (12 ± 2.8 nM) leads to internalization through endocytosis and retention of the ligand and its bound radionuclide within the PSMA-positive tumors (Rajasekaran et al. 2003; Eder et al. 2012) for visualization of PSMA-expressing tissues. GOZ

Figure 1. Structural Formula of Gozetotide



Source: NDA submission

Chemical name of gozetotide = OH-Glu-CO-Lys (Ahx-CC-HBED)-OH

Molecular formula/molecular weight = $C_{44}H_{62}N_6O_{17} \times CF_3CO_2H$ / 947g/mol

The recommended dose of GOZ is 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi) and a mass dose of not more than 25 μ g.

Mechanism of Action

GOZ binds to PSMA and is internalized through endocytosis within the cancer cell.

The Applicant conducted *in vitro* binding and uptake bridging studies to compare two different GOZ formulations, Locametz and the Listed Drug (LD). No significant differences were obtained from the competitive binding and cellular internalization of the Locametz and the LD formulations evaluated in the studies.

Secondary Pharmacology

Gozetotide was negative for binding or activity against a panel of 87 potential targets. Gozetotide

Safety Pharmacology

The *in vitro* data on the effect of GOZ on hERG tail current in HEK-293 (human embryonic kidney) cells demonstrated no potential risk of QT interval prolongation at up to 10 μ M concentration, corresponding to 1000-fold higher than the predicted clinical C_{max} . The *in vivo* safety pharmacology data demonstrated no significant CNS and respiratory effects in rats at up to 0.75 mg/kg (300-fold greater than the clinical dose by BSA scaling) or on cardiac electrophysiological function or hemodynamics as measured by telemetry in conscious minipigs at up to 0.29 mg/kg (690-fold greater than the clinical dose by BSA scaling).

Pharmacokinetics (PK)/Absorption, Distribution, Metabolism, Excretion (ADME) Studies

The distribution studies demonstrated PSMA-dependent specificity and favorable tumor-to-background ratios resulting in effective imaging of PSMA[+] tumor. The data showed retention of radioactivity in the kidneys, and excretion into the bladder and the pharmacokinetics data indicated that GOZ is rapidly cleared from the circulation. Gozetotide was moderately bound to plasma proteins when tested at 1 and 5 μ g/mL concentrations in the human, minipig, rat, and mouse species evaluated. Gozetotide was metabolically stable against enzymatic degradation by kidney S9 fractions from human, rat, and minipig when evaluated during a 1-hour incubation. Mice biodistribution data showed that the primary route of elimination is the renal system. Similarly, the available clinical data demonstrated that the primary route of excretion of GOZ in humans is urinary. No evidence of pharmacodynamic drug-drug interactions were reported with gozetotide.

Toxicology

The Applicant conducted an extended, single dose toxicity study of gozetotide in Sprague Dawley rats to support the application. Gozetotide was well tolerated in male and female rats at up to 1.33 mg/kg, the highest dose level tested and a no-observed-adverse-effect level (NOAEL) of 1.33 mg/kg was obtained in the study. Based on the intended clinical mass dose of not more than 25 μ g, a safety margin of 518X the clinical dose was estimated. The use of GOZ as a microdose does not necessitate a genotoxicity study. Nevertheless, the bacterial mutagenicity potential of gozetotide was evaluated *in silico* by a computational toxicology assessment and the structure did not match any structural alerts or examples for bacterial *in vitro* mutagenicity in DEREK NEXUS Prediction Report. Thus, gozetotide is not predicted to be a bacterial mutagen. Reproductive and developmental toxicity studies were not required for gozetotide; a waiver was granted for the application based on the proposed single-use indication, target population, and microdose.

Recommendation

The nonclinical data in this submission adequately support the approval of Locametz for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology.

The Applicant is relying on Ga 68 gozetotide injection under NDA 212642 and NDA212643 as the listed drug.

5.3. Pharmacology

Primary and Secondary Pharmacology

GOZ binds with high affinity ($K_i = 12 \pm 2.8$ nM) to PSMA-positive prostate cancer cells to allow for PET imaging. In order to evaluate the potential for interaction with different targets, gozetotide, at a concentration of 10 μ M, was evaluated in vitro across a panel of receptors, ion channels, enzymes, and transporters. These 87 targets were selected on the basis of their clinical relevance in humans for the evaluation of off-target effects. Results showed that gozetotide did not interact with the potential targets 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 concentration tested (10 μ M) is approximately 1000-fold higher than the 10 nM theoretical clinical C_{max} of PSMA-11 in patients following an administration of GOZ. The lack of a pharmacologic effect of gozetotide, at concentrations up to 10 μ M, was further demonstrated in an in vitro cytotoxicity assay in PSMA[+] 22RV1 cells and PSMA[-] KB cells. The resulting data showed that there was no significant cytotoxicity observed at any concentration of gozetotide in either cell line. The results of this study provide evidence that gozetotide exposure is unlikely to exert direct pharmacological activity resulting in cytotoxicity. This conclusion is further supported by the lack of adverse effects in safety pharmacology or toxicology studies described below.

The FDA's Assessment:

The review team agrees with the Applicant's position.

The Applicant provided summaries of primary and secondary pharmacology data obtained from peer-reviewed scientific literature to support the NDA. The data from binding studies demonstrated GOZ has high affinity for PSMA-positive prostate cancer cells. The Applicant also conducted in vitro secondary pharmacology studies to evaluate off-target binding (Study # 100053460-3) and cytotoxicity (Study # 0587) of gozetotide. Gozetotide did not demonstrate significant affinity to any of the targets in the panel, supporting the statement that GOZ would be unlikely to demonstrate off-target effects at the clinical dose.

There was a slight trend in decreasing viability observed in PSMA-positive 22RV1 cells with increasing gozetotide concentrations by in vitro cytotoxicity study. The 10 μ M concentration

employed in the study represents a 1000-fold margin above the theoretical gozetotide clinical C_{max} . Thus, gozetotide exposure at physiologically relevant concentrations is unlikely to exert direct pharmacological activity resulting in cytotoxicity.

GOZ Binding And Internalization

An *in vitro* study was conducted to compare two different GOZ formulations, Locametz and the Listed Drug (LD). The competitive binding and internalization of the two formulations of GOZ in PSMA and non-PSMA expressing cell lines (PC-3 PIP and PC-3 Flu, respectively) were investigated at the concentrations of 80 and 22 nM for Locametz and RLD formulation, respectively.

GOZ radiolabeling conditions (e.g., temperature of the reaction) affect the relative proportions of three possible diastereomers: R,R; R,S; and S,S that are formed following complexation with gallium (HBED-CC chelating moiety of Ga 68 gozetotide has two chiral centers). The initial distribution of diastereomers after gallium complexation is temperature-dependent with R,R thermodynamically favored and therefore differences in the labeling conditions may affect PSMA binding and uptake of GOZ. The Applicant conducted an *in vitro* study to compare two different GOZ formulations, Locametz and the LD prepared according to Carlucci G *et al.* (Carlucci *et al.* 2021). Under the high temperature conditions used for synthesis of the LD in this study, 82.4% of the GOZ consisted of isomer 1 (16.9% isomer 2) by reversed phase high performance liquid chromatography (γ -radio detector). In contrast, preparation of GOZ with the Applicant's kit at room temperature, resulted in 62.7% of isomer 1 (37.2% isomer 2). Both formulations demonstrated a highly specific-PSMA binding with similar IC_{50} s (< μ M range). In PC-3 PIP (PSMA expressing) cells, Locametz formulation presented an $IC_{50} = 0.31 \mu$ M ($R^2 = 0.91$) whereas the LD formulation presented an $IC_{50} = 0.89 \mu$ M ($R^2 = 0.93$). The normalized IC_{50} were also calculated based on each formulation's specific activity and reported as 0.42μ M ($R^2 = 0.92$) for Locametz formulation and 0.79μ M ($R^2 = 0.91$) for LD formulation. Locametz formulation presented a cellular internalization of 16% and 21% at 2 hours and 4 hours, respectively, while LD formulation showed a cellular internalization of 13% and 22% at 2 hours and 4 hours, respectively. These studies did not demonstrate a significant difference in the binding affinity or cellular internalization between the Locametz and LD GOZ formulations. Thus, the results of this study demonstrate that differences in GOZ prepared with the Applicant's kit and the LD do not significantly affect binding affinity for PSMA and cellular internalization.

The Applicant's Position:

Safety Pharmacology

Safety pharmacology studies indicate that GOZ is not expected to cause effects on the vital functions of the CNS, respiratory, or cardiovascular systems. In the in vitro hERG patch clamp assay, the mean maximum inhibition was less than 20% at a concentration of 100 μ M, therefore gozetotide was considered to not have an effect on hERG tail current. The negative results in this assay at concentrations up to approximately 10,000-fold higher than the theoretical clinical C_{max} further support the lack of a predicted effect on hERG in the clinical setting. In the in vivo safety pharmacology studies conducted with gozetotide, no adverse effects were observed on CNS or respiratory function in rats, or 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 gozetotide dose tested (0.75 mg/kg), is approximately 300-fold relative to a maximum gozetotide mass dose of 25 µg in an average 1.7 m² patient. With regard to the cardiovascular system in minipigs, the top dose of 0.29 mg/kg is equivalent to an estimated safety margin of approximately 690-fold based on body surface area scaling to the maximum gozetotide mass dose of 25 µg in an average 1.7 m² patient.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions.

The Applicant conducted safety pharmacology studies evaluating CNS, respiratory, and cardiovascular effects of GOZ to support the NDA submission. Studies included an in vitro hERG assay (Study # 20200008PEHPP), CNS and respiratory safety in rats (Study # A3756 and Study # A3757, respectively), and cardiovascular safety in minipigs (Study # A3758). Adequate safety margins were demonstrated in the evaluated safety pharmacology parameters. The available data suggests no CNS, respiratory and cardiovascular concerns at the proposed dose level.

5.4. ADME/PK

The Applicant's Position:

GOZ is administered intravenously, therefore no absorption studies were conducted. PSMA-11 was found to be moderately bound to plasma proteins in all species evaluated (33% to 44%). Blood-to-plasma partitioning ratios of PSMA-11 were lower than 1 in all tested species, indicating that PSMA-11 is not majorly distributed into erythrocytes. In mice, there was rapid clearance from circulation, with limited uptake and retention in normal organs aside from the kidneys. The kidneys of mice, like humans, express PSMA and also represent the route of excretion for 68Ga-PSMA-11. PSMA-11 showed a generally linear toxicokinetic behavior, with increasing systemic exposure and peak plasma concentrations associated with increasing dose levels. The half-life of PSMA-11 was between 0.3 and 0.6 hours, and the volume of distribution indicated a low distribution into tissues compared to the total body water. Metabolic stability was confirmed in plasma, liver S9, and kidney S9, and was relatively consistent across species.

The FDA's Assessment:

FDA generally agrees with the Applicant's summaries of the nonclinical ADME/PK data.

For the *in vitro* PK drug interaction studies (e.g., cytochrome P450 metabolism and transporter studies) see Section 6 for FDA's assessment.

The available PK/ADME data on gozetotide suggested moderate protein binding (33% to 44% in human, rat and minipig), rapid clearance from circulation (half-life ranging from 0.3 hours to 0.6 hours in male and female rats), urinary excretion and metabolic stability of GOZ.

Table 4. Summary of Available Nonclinical ADME/PK Data

Type of Study	Major Findings
Absorption N/A	N/A
Distribution	
<i>Non-GLP PSMA-11 Protein Binding in Human, Rat, and Mini-pig Plasma (Study # 0596)</i>	Gozetotide was moderately bound to plasma proteins when tested at 1 and 5 µg/mL concentrations in the human, minipig, rat and mouse species evaluated. Gozetotide plasma protein binding was approximately 33% at both 1 and 5 µg/mL in human plasma while the PSMA-11 plasma protein binding was 44% and 36% at 1 and 5 µg/mL, respectively in rat plasma. The minipig plasma protein binding for gozetotide was approximately 41% and 38% at 1 and 5 µg/mL, respectively.
<i>Estimation of PSMA-11 Molecule Blood/Plasma Partitioning in Human, Mouse, Rat, Mini-pig, and Dog Bloods (Study # Q19_093)</i>	Blood-to-plasma partitioning of gozetotide was tested at 5 µg/mL and the data showed that the mean blood-to-plasma ratios for gozetotide were 0.54 (mouse), 0.43 (rat), 0.71 (minipig), and 0.71 (human). The blood-to-plasma partitioning values were lower than 1 in all tested species indicating that gozetotide is not majorly distributed into erythrocytes.

Type of Study	Major Findings		
<i>44Sc-PSMA-617 for Radiotheragnostics in Tandem with 177 Lu-PSMA-617-preclinical Investigations in Comparison with 68 Ga-PSMA-11 and 68 Ga-PSMA-617 (Umbricht et al. 2017).</i>	Female, athymic nude Balb/c mice were subcutaneously inoculated with PSMA[+] PC-3 PIP cells on the right shoulder and with PSMA[-] PC-3 flu cells (5 × 10⁶ cells in 100 µL HBSS with Ca²⁺/Mg²⁺) on the left shoulder 2 weeks before the performance of the experiments. GOZ (5 MBq, 1 nmol, 100–200 µL) was administered as a bolus intravenously and the mice were sacrificed at three time points (15, 30, and 60 min) post injection (p.i.). Selected tissues and organs were collected, weighed and radioactivity was measured. The injected GOZ was quickly cleared from the blood. High and rapid accumulation of radioactivity was demonstrated in PSMA[+] PC-3 PIP tumors, with 40% of the injected activity per gram tumor mass quantified at 2 hours post injection. Compared to the uptake and retention observed in the PSMA[+] tumors, the uptake in the PSMA[-] PC-3 flu tumors was approximately 300-fold lower by comparison (0.13% IA/g, 2h p.i.). This data demonstrates the specificity of GOZ. In most normal tissues, the uptake was low, and the clearance was rapid, except for the kidneys, which are a PSMA expressing tissue as shown in the Table below.		
68Ga-PSMA-11 (%IA/g)			
	15 min p.i.	30 min p.i.	2 h p.i.
Blood	5.05 ± 0.58	2.55 ± 0.72	0.08 ± 0.01
Heart	2.45 ± 0.29	1.31 ± 0.19	0.18 ± 0.03
Lung	3.87 ± 0.22	2.23 ± 0.33	0.31 ± 0.10
Spleen	5.33 ± 1.78	4.76 ± 1.13	2.18 ± 0.38
Kidneys	74.7 ± 7.02	86.7 ± 14.6	58.8 ± 7.62
Stomach	1.42 ± 0.15	0.85 ± 0.19	0.35 ± 0.17
Intestines	1.42 ± 0.07	1.20 ± 0.24	0.95 ± 0.86
Liver	2.00 ± 0.32	1.55 ± 0.04	0.56 ± 0.04
Salivary glands	2.73 ± 0.27	1.59 ± 0.18	0.39 ± 0.01
Muscle	1.21 ± 0.11	0.67 ± 0.06	0.06 ± 0.01
Bone	1.85 ± 0.20	0.81 ± 0.14	0.06 ± 0.00
PC-3 PIP	31.5 ± 13.0	49.3 ± 4.97	40.0 ± 2.55
PC-3 flu Tumor	2.19 ± 0.05	1.04 ± 0.17	0.13 ± 0.02
Ratios (tumor to blood or normal tissues)			
Tumor-to-blood	6.10 ± 1.84	20.5 ± 6.40	536 ± 43.7
Tumor-to-liver	15.3 ± 3.96	31.7 ± 2.48	71.3 ± 7.48
Tumor-to-kidney	0.41 ± 0.14	0.58 ± 0.10	0.69 ± 0.12
Values shown represent the mean ± S.D. of data from three animals (n=3) per cohort Tumor-to-background ratios are calculated for the PSMA[+] PC-3 PIP tumor xenografts Source: Umbricht et al 2017			
Source: Sponsor Table 4-1 from Section 2.6.4. Pharmacokinetics Written Summary			

Type of Study	Major Findings
<i>Plasma and Metabolic Stability Studies (Study # 0595).</i>	The stability of NatGOZ (nonradioactive Ga-labeled PSMA-11) was investigated in human, rat, and minipig kidney S9 fractions. In the study, gozetotide was incubated with kidney S9 fractions in phosphate buffer, pH 7.4 at 37°C. The samples were extracted with acetonitrile containing the aminopterin-d5 internal standard and filtered and the filtrates were heated, evaporated, and reconstituted with water prior to LC-MS/MS analysis. Activity of S9 fractions were confirmed by analysis of lauric acid metabolism employed as a positive control. In liver S9 + cofactors, there was a slight decrease in the gozetotide levels observed in the rat and minipig. However similar decreases were seen in the minus cofactor and minus S9 control groups suggesting that the slight loss of analyte is not enzyme specific. Gozetotide was metabolically stable against enzymatic degradation by kidney S9 fractions from human, rat, and minipig when evaluated during a 1-hour incubation. There was little or no degradation in rat or minipig and the maximal decrease in the gozetotide levels was only 12% in human 1-hour incubations in the presence of S9 + cofactors, and a 7% loss with S9 alone at this same timepoint. However, a 15% loss was also observed in the control experiment with no S9 or co-factors. The data demonstrated that gozetotide is metabolically stable against kidney S9 fractions from human, rat, and mini-pig for up to 1 hour. A slight decrease in gozetotide levels observed in the human kidney S9 group over the course of an hour. Similar decreases were demonstrated in the minus cofactor and minus S9 control groups, suggesting that this minor loss of analyte is not enzyme specific. However, a slight loss of lauric acid over the course of an hour was shown following incubation of the positive control compound, lauric acid, in kidney S9 fractions from each species.

Type of Study	Major Findings
Excretion	
<i>44 Sc-PSMA-617 for Radiotheragnostics in Tandem with 177 Lu-PSMA-617- preclinical Investigations in Comparison with 68 Ga-PSMA-11 and 68 Ga-PSMA-617 (Umbricht et al. 2017).</i>	Biodistribution data in mice showed that the primary route of elimination is the renal system with lower uptake in the liver and intestine. Similarly, the available clinical data demonstrated that the primary route of excretion for GOZ in humans is renal.
TK data from general toxicology studies <i>PSMA-11 Single Dose Intravenous Extended Toxicity Study in Rats Conducted by (b) (4) Study # A3755</i>	The toxicity and the TK profile of gozetotide (0.67 and 1.33 mg/kg gozetotide) showed that gozetotide was well tolerated in male and female Sprague Dawley rats with no sex-specific differences in systemic exposure by AUC(0-last) and Cmax. NOAEL: 1.33 mg/kg Safety margin: 518X clinical dose was estimated. T_{1/2}: 0.4 hours (males); 0.3-0.6 hours (females) Systemic exposure by AUC(0-tlast): 1261 and 2042 ng*h/mL (males); 1057 and 2041 ng*h/mL (females) Systemic exposure by Cmax:2396 and 5263 ng/mL (males) and 3124 and 5697 ng/mL (female) T_{max}: 0.083 hours Volume of distribution: 285-370 mL/kg (male); 311-507 mL/kg (female)

Source: *PSMA-11 Single Dose Intravenous Extended Toxicity Study in Rats Conducted by (b) (4) Study # A3755*

Abbreviations: AUC, area under the curve; (b) (4) ; GLP, glucagonlike peptide; LC-MS/MS , liquid chromatography with tandem mass spectrometry; NatGOZ, nonradioactive Ga-labeled PSMA-11; NOAEL, no-observed-adverse-effect-level; PSMA, prostate-specific membrane antigen; TK, toxicology

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

An extended GLP single-dose toxicity and TK study was conducted in male and female Sprague Dawley rats with an unlabeled gozetotide formulation. There were no toxicology studies conducted with the radioactive drug product GOZ, per the relevant guidance. The extended single dose toxicity study of unlabeled gozetotide in rats demonstrated a favorable nonclinical safety profile. No relevant treatment-related toxicologic effects were observed after the single intravenous bolus administration of doses that were up to 530 times higher than the maximum human gozetotide dose (25 µg) based on BSA scaling from rats to humans. Overall, the nonclinical data demonstrated that gozetotide did not induce prohibitive target organ toxicity.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of the toxicology data.

The toxicity and the toxicokinetic profile of gozetotide showed that gozetotide was well tolerated in male and female Sprague Dawley rats. No adverse effects were observed in an extended, single-dose intravenous toxicity study in rats at up to 1.33 mg/kg gozetotide (referred to in the

study report as PMSA-11), providing a 518-fold safety factor over the 25 µg maximum clinical mass dose based on body surface area scaling.

Table 5. Methods of Study No. A3755

Methods	Details
Dose and frequency of dosing	0 (vehicle), 0.67 (LD), 1.33 (HD) mg/kg gozetotide; single dose administration.
Route of administration	Intravenous
Formulation/Vehicle	Gozetotide salt (Batch # AJ0-191111/07, 98.4 % purity), sodium acetate buffer, containing 40 mg/mL of sodium chloride
Species/Strain	Sprague Dawley (SD) rats
Number/Sex/Group	15/sex/group
Age	27-29 days old
Satellite groups	TK satellite, n=9/sex/group for gozetotide and n=3 for vehicle control.
Deviation from study protocol affecting interpretation of results	No

Source: PSMA-11 Single Dose Intravenous Extended Toxicity Study in Rats/ (b) (4) Study No. A3755

Conducting laboratory and location: (b) (4)

Study Title/Number: PSMA-11 Single Dose Intravenous Extended Toxicity Study in Rats/ (b) (4) Study No. A3755

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Abbreviations: HD, high dose; LD, low dose; SD, Sprague Dawley

Table 6. Observations and Results: Changes From Control Study No. A3755I

Parameters	Major Findings
Mortality	No mortality reported
Clinical signs	No changes in the body weight, food consumption, hematology, coagulation, between the control and treated animals were reported.
Body weights	There were no treatment-related effects.
Hematology	No changes in hematology parameters were found.
Clinical chemistry	No changes in biochemical parameters evaluated on Days 2 and 15.
Urinalysis	No significant changes in the urinalysis were reported.
Gross pathology	No changes in terminal body weight of treated animals when compared to the controls, both at interim (Day 2) and final sacrifice (Day 15). For both macroscopic and microscopic observations, no significant differences were reported in treated animals, when compared with controls, both at interim (Day 2) and final sacrifice (Day 15).
Organ weights	No changes in absolute and relative organ weights of treated animals when compared to the controls, both at interim (Day 2) and final sacrifice (Day 15).
Histopathology	No test article related microscopic findings reported at interim (Day 2) or final sacrifice (Day 15) at up to the HD
Adequate battery: Yes	

Source: PSMA-11 Single Dose Intravenous Extended Toxicity Study in Rats/ (b) (4) Study No. A3755

Conducting laboratory and location: (b) (4)

Abbreviations: HD: high dose.

5.5.2. Genetic Toxicology

The Applicant's Position:

GOZ is a microdose radiodiagnostic; therefore no genotoxicity studies were conducted with GOZ or the gozetotide precursor as they are not required according to the Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (August 2018). However, the bacterial mutagenicity potential of gozetotide was evaluated in silico by a computational toxicology assessment of the chemical structure using DEREK and SARAH NEXUS models. The results indicated that gozetotide was not a bacterial mutagen and could be treated as a non-mutagenic compound.

The FDA's Assessment:

FDA does not recommend conduct of genotoxicity studies for microdose radiopharmaceuticals. FDA confirmed the Applicant's results of the submitted computational toxicology assessment and agrees with the conclusions. In the submitted report, the bacterial mutagenicity potential of gozetotide was evaluated *in silico* by a computational toxicology assessment of the gozetotide chemical structure using DEREK and SARAH NEXUS models. The data showed that the structure did not match any structural alerts or examples for bacterial *in vitro* mutagenicity in DEREK. Thus, gozetotide is not predicted to be a bacterial mutagen.

5.5.3. Carcinogenicity

The Applicant's Position:

GOZ is a microdose radiodiagnostic, therefore no carcinogenicity studies have been conducted with GOZ or the gozetotide precursor as they are not required according to the relevant guideline: Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (August 2018).

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not required for this application.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

GOZ is a microdose radiodiagnostic, therefore no reproductive and developmental toxicity studies were conducted with GOZ or the gozetotide precursor as they are not required according to the relevant guideline: Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations (August 2018).

The FDA's Assessment:

No reproductive and developmental toxicology studies for gozetotide were conducted or identified in the peer-reviewed scientific literature. The Applicant requested a waiver for reproductive and developmental toxicology studies. The waiver request was justified because gozetotide is well tolerated and rapidly eliminated and will be administered as a single microdose, corresponding to a sub-pharmacologic dose level. The waiver request was granted

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based on the proposed single-use indication, mass dose, and no evidence of any toxicity or genotoxicity effect.

5.5.5. Other Toxicology Studies

The Applicant's Position:

No additional toxicology studies were conducted.

The FDA's Assessment:

The available nonclinical data has adequately justified the safety of GOZ for the proposed indication and no additional toxicology studies are required.

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant proposes reliance on GOZ Injection approved under NDA 212643 in December 2020 as the listed drug (LD) product. Since the amount of active ingredient is not the same and the inactive ingredients are different in the Locametz and LD products, consultation with the Division of Biopharmaceutics in the Office of New Drug Products concluded that a biowaiver was not applicable and that bridging between Locametz and the LD products needed to be established (refer to OPQ's Biopharmaceutics review). Also, there was no information in the NDA to support that Locametz has been tested in humans. Locametz was not used in the VISION trial; instead several other Ga 68 gozetotide formulations were used. Therefore, the lack of bridging information in the NDA was communicated to the Applicant (DARRTS ID 4854033, 09/09/21). To assure the completeness of the NDA for Agency review, the FDA requested the following bridging information, in addition to comparison of physiochemical properties between the products, be submitted to the NDA:

- Comparative in vitro data for binding and internalization for Locametz and the LD.
- Dosimetry data for Locametz OR
- Comparison of GOZ mass dose between patients who were positive for patient selection for radioligand therapy and patients who were negative for patient selection for radioligand therapy from the currently ongoing Phase 3 studies, PSMAfore and PSMAddition.

In response to FDA's information request, the Applicant submitted the following bridging evidence:

- Comparative analysis of GOZ mass dose between patients who were positive for patient selection and patients who were negative for patient selection for radioligand therapy from PSMAfore and PSMAddition. This analysis is to address whether the amount of "cold" compound affects the clinical performance of the radiolabeled drug, as the mass dose of gozetotide, the active pharmaceutical ingredient, differs between the Applicant's kit and LD product formulations per batch. Up to 25 µg of gozetotide can be delivered in a single patient dose using the Applicant's kit, whereas the LD product can deliver up to a maximum of 5 µg of gozetotide per patient dose. As also discussed in Section 7 of this review, analysis of data from two ongoing phase 3 trials [PSMAfore (CAAA617B12302) and PSMAddition (CAAA617C12301)] that used the Applicant's kit, demonstrated no effect of mass dose within a relevant range on imaging performance. The analysis showed that mass doses values [geometric mean (%CV): 11.7 (55) vs. 15.8 (55) µg] were comparable between PSMA-positive ("eligible": n=95) and PSMA-negative ("ineligible": n=8) patients pooled from the two Phase 3 trials.
- Comparative in vitro data for binding and internalization for Locametz and the LD. This study is to address whether the difference in radiolabeling of gozetotide between the Applicant's kit and the LD product has any impact on drug targeting. Gozetotide supplied in the Applicant's kit is radiolabeled at room temperature whereas the LD product uses an

(b) (4) Reaction temperature affects the ratio of gozetotide diastereomers. Therefore, this difference between the Applicant's kit and the LD product could impact efficacy. The Applicant conducted in vitro cell binding and internalization study of gozetotide between Applicant's Kit and gozetotide radiolabeled at elevated temperature in PSMA-expressing cell lines. As described in Section 5 of this review, the results showed no meaningful difference in PSMA-binding affinity (normalized IC₅₀: 0.42 vs. 0.79 μM) and comparable cellular uptake (% internalization: 16.24% vs, 13.10% at 2 hours, and 21.24% vs. 22.13%) between the two gozetotide formulations, demonstrating adequate in vitro comparability.

Refer to the Biopharmaceutics review for comparison of physiochemical properties between Locametz and LD products.

The above sources of evidence, including comparative biopharmaceutical assessment, the Applicant's in vitro binding/internalization study and evaluation of mass dose and imaging performance using the Applicant's clinical data, together support adequate bridging between the Applicant's kit and the LD drug products.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position

As a radioactive diagnostic agent, the dosimetry and pharmacokinetics of GOZ have been well described based on tracking the positron emissions from this agent rather than the non-radioactive chemical precursor molecule (gozetotide). This is appropriate as the mass dose administered is a microdose and is therefore not pharmacologically relevant. The data included in the application consists of results from in vitro human biomaterial studies (protein binding, blood-plasma ratio, metabolic stability, drug-drug interaction) and literature-derived in vivo clinical pharmacology studies (blood-radioactivity pharmacokinetics and dosimetry). Results from both sources were integrated to characterize the ADME properties of GOZ in humans. These properties were further utilized when assessing intrinsic and extrinsic factors which may affect the PK of GOZ. Lastly, the available literature was used to support the recommended dose (mass and radioactivity) and the use of GOZ in prostate cancer patients.

The FDA's Assessment:

The FDA agrees with Applicant's position based on the information (comparative biopharmaceutical assessment, the in vitro binding/internalization study, and evaluation of mass dose and imaging performance) to support adequate bridging between Locametz and the LD product. Therefore, clinical pharmacology content for Locametz will be derived from the LD product's prescribing information. In addition, the in vitro metabolic stability of gozetotide and the lack of effect of gozetotide on major cytochrome P450 (CYP) enzymes and transporters in vitro will be included in the Locametz labeling based on the in vitro studies provided in the NDA.

6.2.2. General Dosing and Therapeutic Individualization

The Applicant's Position

The recommended dose of GOZ is [REDACTED] (b) (4)
[REDACTED] 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi). (b) (4)
[REDACTED] and
[REDACTED] is also in line with the recently approved GOZ USPIs (Gallium 2020a; Gallium 2020b). (b) (4)
[REDACTED]

In Study PSMA-617-01, GOZ was planned to be administered intravenously at a dose of 111-185 MBq (3 - 5 mCi) [REDACTED] (b) (4)
The actual dose administered to patients in Study PSMA-617-01 ranged from 92.8 MBq (2.5 mCi) to 287.5 MBq (7.8 mCi), with a corresponding body weight adjusted dose range of 0.9-3.7 MBq per kg (median dose: 1.9 MBq/kg). Overall, 149 patients received activity injected-decay corrected dose exceeding 5 mCi (> 185 MBq) with a mean dose of 2.3 MBq/kg in Study PSMA-617-01.

From a safety perspective, [REDACTED] (b) (4)
[REDACTED] for an administered activity of 150 MBq. This level of radioactivity is lower than other PET agents used for prostate cancer imaging and well within the effective dose from a diagnostic CT. For a 7 mCi (259 MBq) dose, [REDACTED] (b) (4)
[REDACTED]

[REDACTED] Additionally, the maximum 25 µg mass dose is in the microdose range, as it is ≤ 100 µg and ≤ 1/100th of the nonclinical NOAEL (August 2018; November 2018).

The FDA's Assessment:

FDA acknowledges the Applicant's position [REDACTED] (b) (4) but recommends a flat dose consistent with the recommended dose for the LD product (111 MBq to 259 MBq). The FDA agrees with the Applicant's proposed dose range (i.e., 111-259 MBq, 3-7 mCi), which is in alignment with recommended dose for the LD product. Also, a flat dose of Ga 68 gozetotide was used in the VISION trial. Therefore, recommended dose for Locametz will be the same as that of the LD product (111 MBq to 259 MBq (3 mCi to 7 mCi) as a bolus intravenous injection).

The Applicant's Position:

6.2.3. Therapeutic Individualization

No therapeutic individualization is required in the proposed indication based on intrinsic factors (body weight, age, race), drug-drug interactions that may affect the disposition of GOZ or in special populations (hepatic or renal impairment). For further details see Section 6.3.2.

6.2.4. Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

An overview of the ADME properties and clinical pharmacokinetics is provided below.

Absorption:

GOZ is administered intravenously, therefore bioavailability is 100% and absorption studies are not applicable.

Distribution:

Plasma protein binding and blood distribution: Results from in vitro studies indicate that GOZ is moderately bound to human plasma proteins. Protein binding was approximately 33% at gozetotide concentrations of 1 and 5 µg/mL. Additionally, the blood/plasma partitioning ratio of the gozetotide at 5 µg/mL in human blood was 0.71, indicating no accumulation in RBCs.

Dosimetry and biodistribution: The biodistribution of GOZ is shown to correspond well to known cellular expression of PSMA, as well as in those organs involved in excretion. In the dosimetry study conducted by (Demirci et al. 2018), the kidneys received highest radiation with a mean absorbed dose of 0.25 mGy/MBq, followed by the salivary glands, urinary bladder wall, lacrimal glands, spleen and liver. Similar findings were reported from the supportive literature, where kidneys received the highest absorbed dose (range: 0.121-0.413 mGy/MBq) followed by the urinary bladder wall (range: 0.057-0.164 mGy/MBq). The fact that kidneys and bladder wall received the highest absorbed doses could be explained by renal excretion of the radiotracer and physiological expression of PSMA in renal proximal tubules (Demirci et al. 2018). The activity decreased significantly in the kidneys with time, likely due to the fast excretion of the compound with urine (Afshar-Oromieh et al. 2013). Based on (Demirci et al. 2018) the mean effective dose of GOZ was 0.0166 mSv/MBq, resulting in an average effective radiation dose of 2.49 mSv for an administered activity of 150 MBq. This reported effective dose is lower than other PET radiopharmaceuticals described in literature (18F FDG, (Pfob et al. 2016)) and similar to other ⁶⁸Ga-labelled PET imaging agents available on the market (e.g. 3.15 mSv/150 MBq for NETSPOT® and SomaKit TOC®) (NETSPOT 2016; SomaKit 2016). The biodistribution of GOZ was not associated with any adverse effects in those tissues, and administration was safe, as reported in PSMA-617-01, and across the supportive literature.

Metabolism:

Results from in vitro metabolism studies showed that gozetotide was metabolically stable against the enzymatic degradation by human liver and kidney S9 fractions for up to 1 hour, indicating negligible metabolism in human.

Excretion:

GOZ shows high rates of renal excretion and excretion into the urinary bladder (Pfob et al. 2016). The urinary bladder uroepithelium and the kidneys received the highest absorbed doses.

Cumulative urinary excretion after 120 minutes post-injection of GOZ accounted for 14% of the administered dose (Green et al. 2017).

Clinical Pharmacokinetics:

GOZ is rapidly cleared from blood, similar to other peptide radiopharmaceuticals, via renal uptake and excretion into the urinary bladder (Herrmann et al. 2015; Pfob et al. 2016). GOZ showed a bi exponential profile in blood, with an early phase resulted in a half-life of 6.5 min (fast component) and a terminal phase with a half-life of 4.4 h (slow component) (Sandgren et al. 2019). Based on the terminal elimination half-life of 4.4 h and considering that the physical half-life of Ga-68 is 68 min, the resulting effective half-life of GOZ is 54 min. In the absence of a reported C_{max}, the highest anticipated injected total peptide concentration in plasma would be 0.01 ng/ml (10 nM) assuming the 25 µg microdose, a plasma volume of 2.5 L and the molecular weight of gozetotide of 947.0 g/mol.

The FDA's Assessment:

The FDA agrees with the applicant's assessment. Based on the scientific bridge between Locametz and the LD product, dosimetry, and clinical pharmacology content for Locametz prescribing information will be derived from that of the LD product. In addition, information (study number) on blood-to-plasma ratios (Q19-093), human plasma binding (0596), and metabolic stability of gozetotide (0592, AAA-019, R0593, and R0595) will be included in the Locametz prescribing information based on the in vitro studies conducted by the Applicant and provided in the NDA .

The Applicant's Position:

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The efficacy and safety results from GOZ, as well as from the supportive literature, provide evidence of the positive benefit-risk of the recommended dose of GOZ ([REDACTED] ^{(b) (4)} [REDACTED] with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi). While no clinical pharmacology information was collected in PSMA-617-01, the recommended radiation dose range is covered by the range of activity that was utilized in that study. As a radioactive diagnostic agent, traditional exposure-response models for safety and efficacy are not applicable, and such clinical pharmacology evaluations were not conducted with GOZ.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment based on the results of the comparative assessment of biopharmaceutical and in vitro binding/internalization assessments, and evaluation of the mass dose and imaging performance based on clinical data. Refer to Sections 5 and 7 of this review for details of those assessments.

The Applicant's Position:

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

The recommended dose of GOZ is a single administration of [REDACTED] (b) (4), with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi). This dose is appropriate for the general population included in the proposed indication, and no dose modifications are required for demographic factors, drug-drug interactions or in special populations. From a radiation exposure perspective, (Demirci et al. 2018) calculated an effective dose of 0.0166 mSv/MBq, resulting in an approximate effective radiation dose of 4.30 mSv for an administered activity of 259 MBq (7 mCi) dose, at the maximum end of the proposed commercial dose range. This radiation exposure is in the range of other standard-of-care radio-diagnostic procedures (e.g. a diagnostic CT scan would lead up to approximately 15-20 mSv) (McCollough et al. 2015; Akin et al. 2017; Martí-Climent et al. 2017; Smith-Bindman et al. 2019). Additionally, the maximum 25 µg mass dose is in the microdose range, as it is ≤ 100 µg and $\leq 1/100$ th of the nonclinical NOAEL (August 2018).

The FDA's Assessment:

FDA acknowledges the Applicant's position [REDACTED] (b) (4) but recommends a flat dose consistent with the recommended flat dose for the LD product (refer to Section 6.2.2 for details). FDA agrees with the Applicant's proposed dose range for Locametz (i.e., 111-259 MBq, 3-7 mCi) which is in alignment with recommended dose for the LD product. While Locametz was not used the VISION trial, other Ga 68 gozetotide formulations used in the VISION trial were administered as flat doses. Therefore, the recommended dose for Locametz will be identical to the LD product and is appropriate for the same indicated patient populations with prostate cancer as the LD drug and for selecting patients with metastatic castration-resistant prostate cancer (mCRPC) for VIP therapy

The Applicant's Position:

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

The pharmacokinetics of GOZ in special populations were not assessed in dedicated studies. However, the effects of intrinsic factors on the pharmacokinetics (or biodistribution) of GOZ were examined based on internal or literature data, where available.

Based on these assessments, no dose adjustment is required for elderly patients, or for patients with renal or hepatic impairment. The effect of body weight on the PK or biodistribution is unknown, however, the available data from public literature demonstrates that a dose range of [REDACTED] (b) (4) results in desirable technical performance of GOZ.

Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

As GOZ is administered intravenously, no food effect is expected.

No clinical drug-drug interaction studies have been conducted.

The absence of meaningful inhibitory or induction effects on human CYP enzymes and absence of inhibitory effects on efflux or uptake transporters indicate no potential for GOZ to cause clinically relevant drug-drug interactions with the investigated metabolic enzymes and transporters at clinical concentrations of GOZ. Given the single dose and single administration of GOZ as a microdose of not more than 25 µg total peptide mass, any other additional drug-drug interactions are not expected.

The FDA's Assessment:

FDA disagrees with the Applicant's position in that the following drug interaction recommendations will be derived from the LD product's prescribing information:

- Section 2.2: If clinically indicated, a diuretic expected to act within the uptake time period may be administered at the time of radiotracer injection to potentially decrease artifact from radiotracer accumulation in the urinary bladder and ureters.
- Section 7: Androgen deprivation therapy and other therapies targeting the androgen pathway can result in changes in uptake of gallium Ga 68 gozetotide in prostate cancer. The effect of these therapies on performance of gallium Ga 68 gozetotide PET has not been established.

FDA agrees with the Applicant's position regarding inclusion of in vitro information on the lack of effect of gozetotide on major CYP enzymes and transporters in the Locametz labeling based on the in vitro studies provided in the NDA submission.

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 7. 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								
VISION	NCT03511664	Prospective study, open-label, multicenter, randomized Phase 3 study of VIP in the treatment of patients with progressive PSMA-positive mCRPC	111-185 MBq (3-5 mCi) GOZ single i.v. injection; PET imaging 50-100 min p.i. Arm 1: VIP + BSC/BSoC: 7.4 GBq ($\pm 10\%$) VIP 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: BSC/BSoC as per physician's discretion and protocol at the institution	Alternate primary rPFS and OS for randomized treatment; VISION studies of GOZ performance Safety (GOZ): Exposure Demographics Concomitant medications AEs	Subjects treated with a single dose of GOZ and safety monitored for 6 days	1003 patients received GOZ 831 randomized 2:1 to either VIP + BSC/BSoC or BSC/BSoC alone	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).

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
Other studies pertinent to the review of efficacy or safety								
PSMAfore (ongoing)	NCT04689828	Prospective study, open-label, multicenter, randomized Phase 3 trial of VIP in the treatment of taxane naïve men with progressive mCRPC	111-185 MBq (3-5 mCi) GOZ single i.v. injection; PET imaging 50-100 min p.i. Arm 1: VIP + SoC: 7.4 GBq (±10%) VIP iv every 6 weeks (±1 week) for a maximum of 6 cycles Arm 2: ARDT Only. Upon radiographic progression, allowed to crossover to VIP	Primary endpoint rPFS for randomized treatment; safety of VIP	Subjects receive dose of VIP once every 6 weeks for up to 6 cycles. All followed for 30 days after treatment. Long term follow-up until death, loss to follow up, withdrawal of consent	450 planned (225 per treatment group); At bridging data cut-off date (9/24/2021), 70 received GOZ.	Adult male with mCRPC cancer who were previously treated with another ARDT as last treatment and have not been exposed to a taxane-containing regimen in the CRPC or HSPC settings and who are considered appropriate for delaying taxane-based chemotherapy	Multiple sites

Multi-disciplinary Review and Evaluation

NDA 215841, Locametz/gallium Ga 68 gozetotide

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
PSMAddition (ongoing)	NCT04720157	Prospective study, open-label, multicenter, randomized Phase 3 trial of VIP in the treatment of patients with metastatic hormone sensitive PC	111-185 MBq (3-5 mCi) GOZ single i.v. injection; PET imaging 50-100 min p.i. Arm 1: VIP + SOC: 7.4 GBq (±10%) VIP iv every 6 weeks (±1 week) for a maximum of 6 cycles + SOC Arm 2: SOC Only: Upon radiographic progression by BICR, crossover to VIP + SOC	Primary endpoint rPFS for randomized treatment; safety of VIP	Subjects receive dose of VIP once every 6 weeks for up to 6 cycles. All followed 30 days after treatment. Long term follow-up for a period of approximately 12 months	1126 patients planned; At bridging data cut-off date (9/24/2021), 33 received GOZ.	Adult male patients with treatment-naive or minimally-treated mHSPC and candidate for hormonal therapy	Multiple sites

Source: NDA215841\0000, NDA215841\0013

Abbreviations: BICR: blinded independent central review ; GOZ, Ga68-gozetotide; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SOC, standard of care; VIP, Lu177-vipivotide tetraxetan

7.2. Review Strategy

The FDA's Assessment:

Since use of GOZ for patient selection is intended to improve patient outcomes only indirectly (i.e., upstream of the direct therapeutic action of VIP), this review team's focus for patient selection efficacy is on VISION's imaging studies (see sections titled "VISION study..." below), plus coordination with the lead review team for VIP, to whom evaluation of the trial's primary endpoint results is generally deferred. Notably, for this NDA, it is reasonable to anticipate that in the event the lead review team found rPFS and/or OS results to be inadequate, this review team would also find substantial evidence lacking to support the efficacy of Locametz for Pluvicto patient selection. For additional information on patient outcome endpoints in the VISION trial, refer to FDA's Multi-disciplinary Review and Evaluation for Pluvicto.

Table 7 describes PSMAfore and PSMAAddition trials under the Clinical Pharmacology heading because clinical pharmacology data from these trials was reviewed in combination with comparative in vitro data to support a scientific bridge between the Applicant's formulation of GOZ and the LD. See the table for review of the relevant clinical information from these ongoing trials, in which GOZ in the same formulation as Locametz is being used to select patients with metastatic prostate cancer for treatment with Pluvicto. For bridging review, refer to Nonclinical Section 5.3 and Clinical Pharmacology Section 6.2.

Since the review team found that the submitted data was adequate to support a scientific bridge, reliance on FDA's findings for the LD provide substantial evidence to support the Applicant's proposed disease detection indications. Applicant positions not relevant to the statistical and clinical evaluation of the patient selection indication under review were therefore not assessed and omitted.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

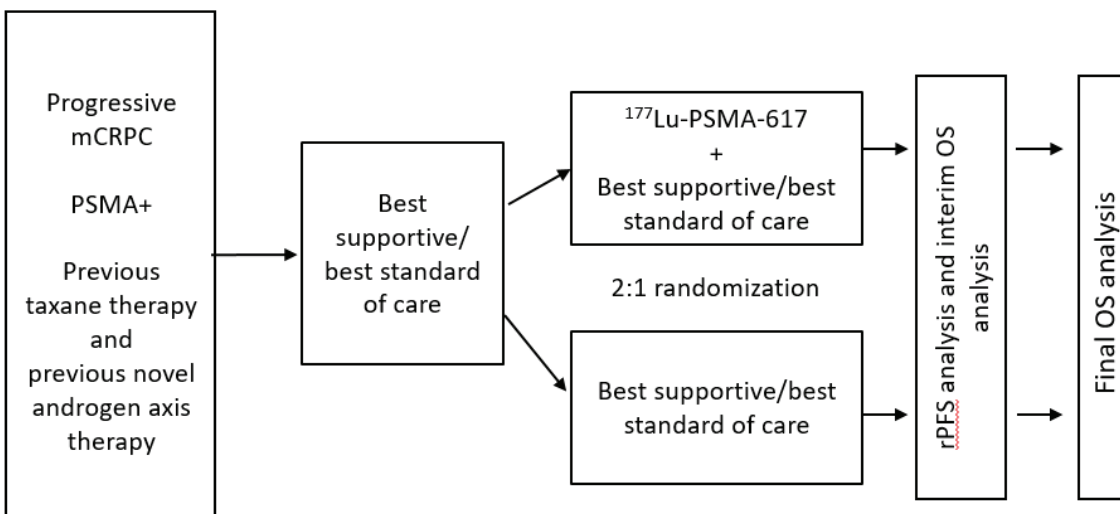
8.1.1. PSMA-617-01 – VISION Trial

The Applicant's Position:

Trial Design

Study PSMA-617-01 is a Phase 3, open-label, international, randomized study to evaluate the efficacy and safety of VIP in patients with progressive PSMA-positive mCRPC, when administered in addition to best supportive care/best standard of care (BSC/BSoC) as compared to BSC/BSoC alone (Figure 1).

Figure 2. VISION Trial Design



Source: NDA215841\0000\m1\us\fdareponse-multidisciplinary-assessment-aid.docx

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival

Trial Location

Study PMSA-617-01 randomized 831 patients involving 82 sites across 8 countries in North America and Europe; 45 of the 82 sites were in the United States; however, this does not raise issues with respect to applicability of the results to the U.S. populations. A sub-study was conducted in Germany involving 4 sites.

Choice of Control Group

Not applicable for GOZ.

Diagnostic and Key Inclusion/Exclusion Criteria

GOZ was used to determine patient eligibility based on PET imaging patterns defined by the central read criteria. Only patients with at least one PSMA scan-positive lesion identified on PSMA-PET/CT and no PSMA scan-negative lesion fulfilling the exclusion criteria were to be enrolled in the study, provided all other inclusion criteria were met. During the central read, the reader's visual assessment of the image resulted in either the patient being eligible (inclusion case) or ineligible (exclusion case) for enrollment.

Eligible adult male patients who had histological, pathological, and/or cytological confirmation of PC, progressive mCRPC (based on any one of the following as defined by the prostate cancer clinical trials working group 3 (PCWG3) criteria for clinical trial entry: serum PSA progression, soft-tissue progression, or progression of bone disease), had received at least 1 novel androgen axis drug (NAAD), were previously treated with at least 1 but no more than 2 prior taxane regimens.

Dose Selection Criteria

The recommended dose of GOZ is (b) (4) with a minimum dose of 111 MBq (3 mCi) up to a maximum dose of 259 MBq (7 mCi). In Study PSMA-617-01, GOZ was planned to be administered intravenously at a dose of 111-185 MBq (3 - 5 mCi) (b) (4)

Study Treatments, Assignment to Treatment, Blinding

At screening, potential patients were assessed for eligibility and had to undergo a GOZ 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:

- *VIP plus BSC/BSoC*
- *BSC/BSoC alone*

This was an open-label study.

Dose Modification, Dose Discontinuation

Each patient received a single dose of GOZ, which is appropriate for the population of intended use, in which PSMA PET imaging will be performed once.

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 clinical 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 IDMC safeguarded patient interest in the study, comprising 2 oncologists, 1 nuclear medicine expert and one biostatistician. The IDMC was responsible for reviewing the overall 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 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

Each patient received a single dose of GOZ. Baseline GOZ PET/CT scan was done within 4 weeks (+ 2 weeks) prior to CID1 but not within 6 days prior CID1. The Sponsor's central reader review of GOZ PET/CT scans determined eligibility for study inclusion.

The FDA's Assessment:

The review team's understanding of the design of the VISION trial – foundational to assessment both of Pluvicto and Locametz for patient selection – generally aligns with the Applicant's position in this section. For additional information, refer to Section 8 of FDA's Multi-disciplinary Review and Evaluation for Pluvicto.

The review team does not agree with the Applicant's position regarding the recommended dose of GOZ. For additional information, refer to Section 6.2.2 of this review.

In the VISION trial, GOZ was used to select patients for treatment with VIP. Study planning documents titled "Imaging Manual" and "Imaging Charter" were prepared by a CRO ((b) (4)) and submitted under IND prior to NDA submission. The documents described the acquisition and interpretation of imaging data underlying VISION trial endpoints, including rPFS.

The acquisition parameters for GOZ PET are summarized in Table 8.

Table 8. GOZ PET/CT Acquisition Parameters

Acquisition Parameters	Summary
Patient preparation	No fast; well hydrated before the study and void immediately before imaging acquisition; furosemide administration optional
Dose and administration route	Intravenous bolus of 3-5 mCi (111-185 MBq)
Acquisition start time	60 min (50-100 min) post injection
Preferred mode	List Mode; 3D or Time of Flight
Patient position	Supine
Scan coverage	Start from mid-thigh to the skull base
Scan speed	2-4 min/bed position
Image reconstruction	Iterative reconstruction preferred
Reconstruction matrix	128x128 or greater

Source: The Applicant's submission under NDA215841\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pc\5351-stud-rep-contr\psma-617-01\psma-617-01--protocol.pdf

The charter also specified that the interpretation of a single central reader (R0) be used to determine VIP eligibility for all patients who provided informed consent for participation in the VISION trial and completed baseline image acquisition procedures. According to the charter, the R0 reader came from a central pool of 3 readers, identified as one reader in the submitted datasets. The R0 reader interpreted baseline GOZ PET/CT in conjunction with post-contrast CT and/or MRI of the chest, abdomen, and pelvis. For subjects with a history of CNS metastasis, brain MRI and/or CT was also presented.

The R0 reader was blinded to baseline bone scans and additional clinical information, including local radiology assessments. No post-baseline or local baseline GOZ data was acquired per protocol or submitted under the Locametz or Pluvicto NDAs. For increased generalizability, consideration of this issue may be warranted in the future.

Figure 3 summarizes the patient selection criteria. The charter defined GOZ positive (VIP eligible) as imaging from any subject for whom the reader found all of the four patient selection criteria listed below to be true. The charter defined GOZ negative (VIP ineligible) as imaging from any subject for whom the reader found at least one of the four selection criteria to be false.

Figure 3. Patient Selection Criteria for Readers Interpreting GOZ PET Imaging in the VISION Trial

A. Any lesion criterion: 1. Any one metastatic lesion in the patient is hyperintense compared to normal liver
B. All lesions $\geq$ size criteria: 2. All of the patient's lymph node metastases $\geq$ 2.5 cm in short axis are hyperintense compared to normal liver 3. All of the patient's bone metastases with soft tissue component $\geq$ 1.0 cm in short axis are hyperintense compared to normal liver 4. All of the patient's solid organ metastases $\geq$ 1.0 cm in short axis are hyperintense compared to normal liver

Source: Adapted from the Applicant's submission under NDA215841\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pc\5351-stud-rep-contr\psma-617-01\psma-617-01--protocol.pdf

In addition, for each of the All Lesions $\geq$ Size criteria (items 2, 3, and 4 under B), the R0 reader was required to annotate at least one false lesion if the criterion was found to be false; if no lesion was found exceeding size criteria, the reader recorded "N/A-No lesion meets size requirement."

Under labeling Section 2.8 (“Imaging Interpretation”), the review team and Applicant have agreed that prescribing information should provide sufficiently detailed information for prescribers, including imaging prescribers, who wish to use Locametz to select patients consistent with how they were selected to provide substantial evidence for approval (excerpt from labeling below):

- For patient selection, interpret LOCAMETZ Z PET in conjunction with patients’ clinical history and imaging from other modalities, including diagnostic anatomical imaging in clinically relevant regions, such as chest, abdomen, and pelvis. On LOCAMETZ PET images, compare uptake of gallium Ga 68 gozetotide at sites of suspected prostate cancer (lesions) with uptake in normal liver. Lesions should be considered positive if gallium Ga 68 gozetotide uptake is greater than normal liver and negative if gallium Ga 68 gozetotide uptake is less than or equal to normal liver.
- Patients should be considered eligible for lutetium Lu 177 vipivotide tetraxetan therapy if at least one tumor lesion is positive and all lesions on anatomical imaging larger in short axis than size criteria are also positive [size criteria: organs $\geq$ 1 cm, lymph nodes $\geq$ 2.5 cm, bones (soft tissue component) $\geq$ 1 cm]. Patients should be considered ineligible for lutetium Lu 177 vipivotide tetraxetan therapy if all lesions are negative or any one lesion larger than size criteria is negative.

The Applicant’s Position:

Trial Endpoints

The primary objective of this study was to compare the two alternate primary endpoints of rPFS and OS in patients with progressive PSMA-positive mCRPC who received VIP in addition to BSC/BSoC compared with patients treated with BSC/BSoC only. Key secondary endpoints were defined in line with Prostate Cancer Working Group 3 as well as FDA and EMA guidance, and included ORR, DCR, and time to first SSE.

For patients screened with GOZ PET, AE monitoring continued up to and including 6 days after administration of GOZ. The treatment-emergent period was defined as the period from the date of GOZ dosing up to 6 days after the date of GOZ dosing as long as this was prior to Cycle 1 Day 1 (CID1). AEs reported as related to the study drug may have been related to either GOZ or BSC/BSoC as the causal relationship between the event and a particular drug was not captured separately in the clinical database.

The FDA’s Assessment:

The review team agrees that evaluation of the benefit of VIP after patient selection with GOZ primarily depends on patient outcome endpoints rPFS and OS. Refer to Section 7.2 for description of coordinated review strategy.

Regarding the Applicant’s position on the 6-day AE monitoring period, outside of stochastic radiation risks shared by diagnostic radiopharmaceuticals as a class, no delayed toxicity is expected with GOZ at the proposed activity and mass dose and based on available data and reported experience. Nevertheless, for GOZ in the context of patient selection, the review team notes that the causality assessment limitations noted by the Applicant could theoretically contribute to over-estimation of acute and sub-acute risk and under-estimation of delayed risk.

The Applicant's Position:

Statistical Analysis Plan and Amendments

The SAP was agreed upon and finalized prior to the conduct of any efficacy analysis and unblinding of the database. The statistical plan was amended two times during the study to reflect changes in protocol design (see Section "Protocol Amendments"). None of the changes to the SAP were related to the GOZ analyses.

Safety Analysis

All safety analyses of GOZ were based on the PSMA-11 safety analysis set which consisted of all subjects who received at least one dose of GOZ. 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, safety topics of interest (including AESI), and the number (%) of subjects with baseline laboratory data, clinically notable vital sign abnormalities, and notable ECG abnormalities were summarized. Safety summary tables included "on-treatment" events/assessments, i.e. those collected on or after the first date of GOZ and collected no later than 6 days after the date of dose administration.

Protocol Amendments

The study protocol was amended 8 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). A detailed discussion of these amendments is provided in Table 9.

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.

Table 9. 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.

Version No. (Date)	Summary of Changes
3.0 (01-Apr-2019) Approved by IEC/IRB	Clarified start and end timing for GOZ TEAEs, VIP TEAEs and BSC/BSoC dosing and intervention TEAEs. 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. 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 GOZ 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 GOZ TEAEs, VIP 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 (VIP + BSC/BSoC) of approximately 30 patients from selected sites in Germany.

Version No. (Date)	Summary of Changes
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 Updated Medical Officer email address Minor updates after review by the country investigator to the following sections to provide further clarity in regard 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
4.3 (04-Jun-2020) Approved by IEC/IRB	
4.4 (22-Jul-2020) Approved by IEC/IRB	
4.4 (22-Jul-2020) Approved by IEC/IRB	

Source: NDA215841\0000\m1\us\fdareponse-multidisciplinary-assessment-aid.docx
 Abbreviations: AE, adverse event; BSC/BSoC, best supportive/best standard of care; DE, Germany; ECG, electrocardiogram; GB, Great Britain; GOZ, Ga68-gozetotide; IEC/IRB, Independent Ethics Committee/Institutional Review Board; ITT, intent to treat; LTFU, long-term follow-up; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PK, pharmacokinetics; QoL, quality of life; rPFS, radiographic progression-free survival; SAE, severe adverse event; TEAEs, treatment emergent adverse events; VIP, Lu177-vipivotide tetraxetan

The FDA’s Assessment:

The team has identified no review issues with the Applicant’s position in this section.

VISION Study of GOZ Reliability for Patient Selection

The Applicant’s Position:

The PSMA-617-01 Reviewer Variability Study was an independent study of the Study PSMA-617-01 scans to assess the extent of inter-reader variability and intra-reader reproducibility of the GOZ PET/CT scans that were collected and utilized in Study PSMA-617-01. As such, there is no separate protocol for the Reviewer Variability Study; for further details of the PSMA-617-01 study design, please refer to Section 8.1.1.

Visual assessment was retrospectively performed in a blinded fashion by three independent and experienced readers on a subset of GOZ PET/CT scans and corresponding diagnostic CT/MRI scans from Study PSMA-617-01.

A total of 125 cases were randomly selected, including 75 cases from patients who met eligibility based on imaging (inclusion cases) and 50 cases from patients who were excluded from enrollment based on the Study PSMA-617-01 read criteria (exclusion cases). Twenty of the 125 cases, including 12 inclusion and 8 exclusion cases, were recoded for repeat reads by the three readers for the evaluation of intra-reader reproducibility. The results from this reader variability study were also compared to the Study PSMA-617-01 eligibility read results that determined the patients’ enrollment into the clinical trial.

Primary Objective: *To evaluate the inter-reader variability of GOZ images among 3 independent, blinded reviewers*

Secondary objective: *To evaluate the intra-reader reproducibility of GOZ images within each of 3 independent, blinded reviewers. 20 cases were recoded for repeat reads to assess intra-reviewer variability.*

Overall inter-reader variability was assessed using Fleiss' Kappa (κ) statistics across all three independent readers, and pairwise variability was analyzed by Cohen's κ statistics in pairs of readers. The sample size of 125 subjects provided 85% power with an assumed Fleiss' κ equal to approximately 0.70 and a null κ of 0.52. Intra-reader reproducibility was evaluated using Cohen's κ analyses. Concordance between the read results from this reviewer variability study and Study PSMA-617-01 eligibility determination was assessed, based on agreement rates.

The FDA's Assessment:

Interval (CI) for Fleiss' kappa exceeded 0.52. Study design was pre-specified and refined over the course of multiple meetings with the Applicant in their role as sponsor of the imaging IND and prior to the completion of the VISION trial. Planning work product included a document prepared by a CRO (b) (4) and titled "Independent Review Charter: Reviewer Variability Study" and a statistical analysis plan.

To measure inter-reader variability, the charter specified that the imaging interpretations of three central re-readers be compared internally with one another. Interpretations were dichotomous and made independently, based on the same imaging, level of blinding, and logical definitions of positive and negative as provided to the original (R0) reader. On the other hand, notable differences between reads and re-reads involved definition phrasing, annotation instructions, and the requirement to record regions in which no lesions exceeding size requirements were found. In addition, whereas the R0 reader addressed all four criteria for each subject, re-readers moved on to the next subject as soon as one of the four read criteria was found to qualify the subject as negative (i.e., VIP ineligible).

Limitations of this study design included these minor differences between original reading and re-reading methods. More fundamentally, reader agreement performance alone is generally insufficient to establish efficacy for a new imaging agent indication. For example, agreement might be high but diagnostic performance against a truth standard unacceptably low. In addition, the kappa study and VISION trial were not independent investigations. For these reasons, the review team did not consider the kappa study adequately designed to stand alone. Rather, it was considered suitable as a source of confirmatory evidence for patient selection, with the term "confirmatory" here in reference to a primary finding of effectiveness based on patient outcomes in the VISION trial (see above).

In addition, for this NDA, the lack of a truth standard in the kappa study was also offset by its presence in association with the efficacy findings relied on for approval of the LD under the 505(b)(2) pathway. In particular, under NDAs 212642 and 212643, FDA found that GOZ can be used effectively by PET readers to detect disease, including distinguishing between normal and metastatic lymph nodes. This finding was based on investigation of patients undergoing pelvic lymph node dissection during prostatectomy, a solid truth standard. For patients farther along in the course of disease, with PSA recurrence, FDA also found that GOZ can be effectively used by PET readers to detect disease. This finding was based on investigation of patients having at least one region containing a positive lesion on imaging and also a matching positive region according to a composite reference standard. Though supportive in the case of this NDA, as a general matter, it should not be assumed that the number of studies directly or indirectly involving diagnostic performance measured against a truth standard need be the same for all NDAs that seek a patient selection indication.

VISION Study of Imaging and Outcomes

The VISION study of imaging and outcomes (quantitative analysis study) involved additional analysis of data from a subgroup of subjects enrolled under the VISION trial. The aim of the study was to learn whether subjects with more versus less PET activity on baseline GOZ imaging responded more versus less favorably to VIP therapy.

During investigational planning meetings with the Applicant in their role as GOZ imaging IND sponsor, the review team was concerned about relying on the kappa study alone as a single source of confirmatory evidence for the proposed patient selection indication. The team's concern arose from at least three considerations. First, the logic of "true, true, unrelated" suggested the possibility that (i) GOZ could be found reliable for VIP patient selection and (ii) VIP could be found effective for treating GOZ-selected patients, but that (i) and (ii) might be independent. Second, the Sponsor's co-development was sparse on early-phase exploratory studies, including no studies in which patients underwent GOZ imaging at baseline but received VIP regardless of the imaging results. Finally, a clear association between response to Lu177-DOTATE and baseline PET activity on In111-pentretotide imaging appeared to be lacking in published analyses of the NETTER-1 trial. For these reasons, to support a new patient selection indication, the review division encouraged the Applicant to pursue a second prospective study of imaging and outcomes under the VISION trial.

The Applicant agreed, providing a study planning document prepared by a CRO (b) (4) titled "Independent Review Charter: Quantitative Analysis," as well as a statistical analysis plan, submitted under the imaging IND and prior to completion of the VISION trial. The study was considered exploratory because of the lack of preliminary data needed to parametrize and agree on any null hypothesis. Classification as "exploratory" also meant that even results found to be supportive would likely also be found premature for labeling. In this context, "supportive" was intended to mean a qualitative assessment by the review team along the lines that for a preponderance of quantitative associations explored between imaging and outcomes, higher and/or less variable baseline PET signal would be found in subjects with favorable outcomes and specific to VIP therapy. The review team also agreed that a supportive result from this study, even if premature for labeling, could nevertheless serve a useful role in generating hypotheses toward new confirmatory investigation and for addressing potential gaps in the combined VISION trial and kappa study results.

Refer to Section 9.1 for statistical review of the quantitative study analysis plan. In brief, all GOZ PET/CT imaging was provided to the imaging CRO for semi-automated tumor segmentation and SUV measurement. The charter specified that only the subset of subjects randomized to the investigational arm would be included in the analysis set. Additional methodological detail was added in the study report. A 41% threshold was applied around the local SUV maximum of each lesion, followed by manual editing, if needed, to yield a volume of interest (VOI). For each VOI, the outlined volume and mean and max standardized uptake value (SUV_{mean} and SUV_{max}) were measured. SUV is intended to represent a multiplicative factor (unitless) indicating the number of photon sources within the location and time measured relative to the number that would be expected if all of the administered radiopharmaceutical distributed evenly throughout the body. Software including VivoQuant, MIM Premier, and AntsRNet was used to guide classification of each VOI into four mutually exclusive compartments labeled

bone, liver, lymph node, and soft tissue (non-liver). Imaging parameters were then explored for associations against patient outcome endpoints, including rPFS, OS, ORR, and PSA response.

VISION Study of Dosimetry and Locametz Dosimetry

The VISION study of dosimetry (dosimetry study) involved additional acquisition of data from a subgroup of subjects enrolled under the VISION trial. The study was performed to estimate radiation absorbed dose following administration of VIP.

The dosimetry study represented a late add-on to the main VISION trial. The study protocol was added as Appendix 12 (“Dosimetry, PK and ECG sub-study design”) under Version 4.4 DE of the main trial protocol, first received on June 11, 2021, after study enrollment had completed. More detailed protocol information was provided under a document titled “PSMA-617 sub-study manual,” submitted under the original submission for NDA 215843. The dosimetry study report was submitted in a file named “psma-617-01—vital-signs.pdf,” including under the original submission for NDA 215841. The dosimetry study report was prepared by a CRO ((b) (4)) and relied on primary data acquired by other CROs ((b) (4)) for VIP imaging and ROI analysis; (b) (4) for handling and analysis of blood and urine samples). The Applicant also submitted complete dosimetry datasets during the review cycle.

Dosimetry study subjects were only assigned to the treatment arm (not randomized). Other than the dosimetry procedures described below, study subjects underwent the same GOZ evaluation and were treated and evaluated in a manner consistent with all other subjects in the VISION trial.

Dosimetry estimates for VIP were determined based on acquisition and analysis of whole body conjugate planar and SPECT-CT imaging in combination with blood and urinary sample assays. Imaging was obtained at approximately 1-2 h, 18-26 h, 36-48 h, and 156-168 h post injection. Outlines of regions of interest (ROIs) were drawn on the planar images for brain, GI, heart, kidneys, lacrimal glands, liver, lungs, salivary glands, image reference standard, thyroid, and whole body. For kidneys, liver, and spleen, ROIs were also drawn on the cross-sectional images and yielded patient-specific volumes for these organs. Gamma scintigraphy detection events corresponding to each ROI were counted to determine bio-kinetic (time-activity) data. Red marrow activity was estimated based on assay of blood samples. Kinetic data were modeled to estimate normalized disintegration numbers. OLINDA EXM v2.2 software parameters included selection of the human alimentary and urinary voiding bladder models and a voiding interval of 3.5 h.

8.1.2. Study Results

VISION Trial

The Applicant’s Position:

In Study PSMA-617-01, potential patients were assessed at screening for eligibility and had to undergo a GOZ PET/CT scan to evaluate PSMA positivity per the pre-defined read rules, by the central reader. Only patients with GOZ PET/CT scans and meeting all other inclusion/exclusion criteria were randomized. In total, 831 patients were randomized in the study, 551 to the VIP + BSC/BSoC arm and 280 to the BSC/BSoC only arm.

Study PSMA-617-01 showed the clinical relevance of GOZ PET scans for determination of patient eligibility to PSMA-targeted therapy with VIP. Clinical benefit was conferred to patients who received VIP plus BSC/BSoC relative to those receiving BSC/BSoC alone.

(b) (4)

The FDA's Assessment:

Starting with the 1218 patients who provided informed consent to be subjects under the VISION trial, 1040 and 559 (non-dosimetry: 1003 and 529) were administered GOZ and VIP, respectively. GOZ preceded administration of VIP in all subjects who received VIP (mean 22 days, range 6 to 93). For 995 of the 1003 subjects who received GOZ, imaging for patient selection was interpreted as positive (eligible) or negative (ineligible) for VIP by the R0 reader (see Figure 3 for positivity definition). Of the 995 subjects, the R0 reader found 869 subjects to be positive (eligible, 87%) and 126 subjects to be negative (ineligible, 13%) for patient selection.

Regarding the Applicant's position on the clinical benefit of VIP downstream of patient selection, for a full description and FDA's assessment, refer to Section 8.1.2 of FDA's Multi-disciplinary Review and Evaluation for Pluvicto. The indented passage below from the prescribing information for Pluvicto summarizes FDA's assessment that the trial's primary and key secondary endpoints (OS/rPFS and ORR, respectively) demonstrated superior outcomes in the VIP + BSC/BSoC arm compared to in the BSC/BSoC arm.

The efficacy of PLUVICTO was evaluated in VISION (NCT03511664), a randomized (2:1), multicenter, open-label trial that evaluated PLUVICTO plus BSoC (N = 551) or BSoC alone (N = 280) in men with progressive, PSMA-positive mCRPC. 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. 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.

Patients received PLUVICTO 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 ketoconazole; radiation therapy to localized prostate cancer targets; bone-targeted agents; androgen-reducing agents; AR pathway inhibitors. Patients continued treatment for up to 4-6 doses, or until disease progression or unacceptable toxicity. Patients with stable disease or partial response after 4 doses of PLUVICTO plus BSoC received up to 2 additional doses per investigator's discretion.

The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 years (range, 40 to 94 years); 87% White; 7% Black or African American; 2.4% Asian; 92% had ECOG PS0-1; 8% had ECOG PS2. All

patients had received at least one prior taxane-based chemotherapy regimen and 41% of patients received two. One prior AR pathway inhibitor had been administered to 51% of patients, 41% of patients received 2, and 8% of patients received 3 or more. During the treatment period, 53% of patients in the PLUVICTO plus BSoC arm and 68% of patients in the BSoC alone arm received at least one AR pathway inhibitor.

The major efficacy outcome measures were overall survival (OS) and radiographic progression-free survival (rPFS) by blinded independent central review (BICR) per Prostate Cancer Working Group 3 (PCWG3) criteria. An additional efficacy outcome measure included was overall response rate (ORR) by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

VISION demonstrated a statistically significant improvement in both major efficacy outcome measures of OS and rPFS by BICR with PLUVICTO plus BSoC compared to treatment with BSoC alone.

Efficacy results for VISION are presented.

Pluvicto Efficacy Results in VISION

	PLUVICTO Plus BSoC	BSoC
Overall Survival (OS)	N = 551	N = 280
Deaths, n (%)	343 (62%)	187 (67%)
Median, months (95% CI) ^a	15.3 (14.2, 16.9)	11.3 (9.8, 13.5)
Hazard ratio (95% CI) ^b	0.62 (0.52, 0.74)	
P-value ^c	< 0.001	
Radiographic Progression-Free Survival (rPFS)	N = 385	N = 196
Events (progression or death), n (%)	254 (66%)	93 (47%)
Radiographic progressions, n (%)	171 (44%)	59 (30%)
Deaths, n (%)	83 (22%)	34 (17%)
Median, months (95% CI) ^a	8.7 (8.3, 10.5)	3.4 (2.4, 4.0)
Hazard ratio (95% CI) ^b	0.40 (0.31, 0.52)	
P-value ^c	< 0.001	
Overall Response Rate (ORR)		
Patients with evaluable disease at baseline	N = 319	N = 120
ORR (CR + PR), n (%)	95 (30%)	2 (2%)
(95% CI)	(25%, 35%)	(0%, 6%)
Complete response (CR), n (%)	18 (6%)	0 (0%)
Partial response (PR), n (%)	77 (24%)	2 (2%)
P-value ^d	< 0.001	

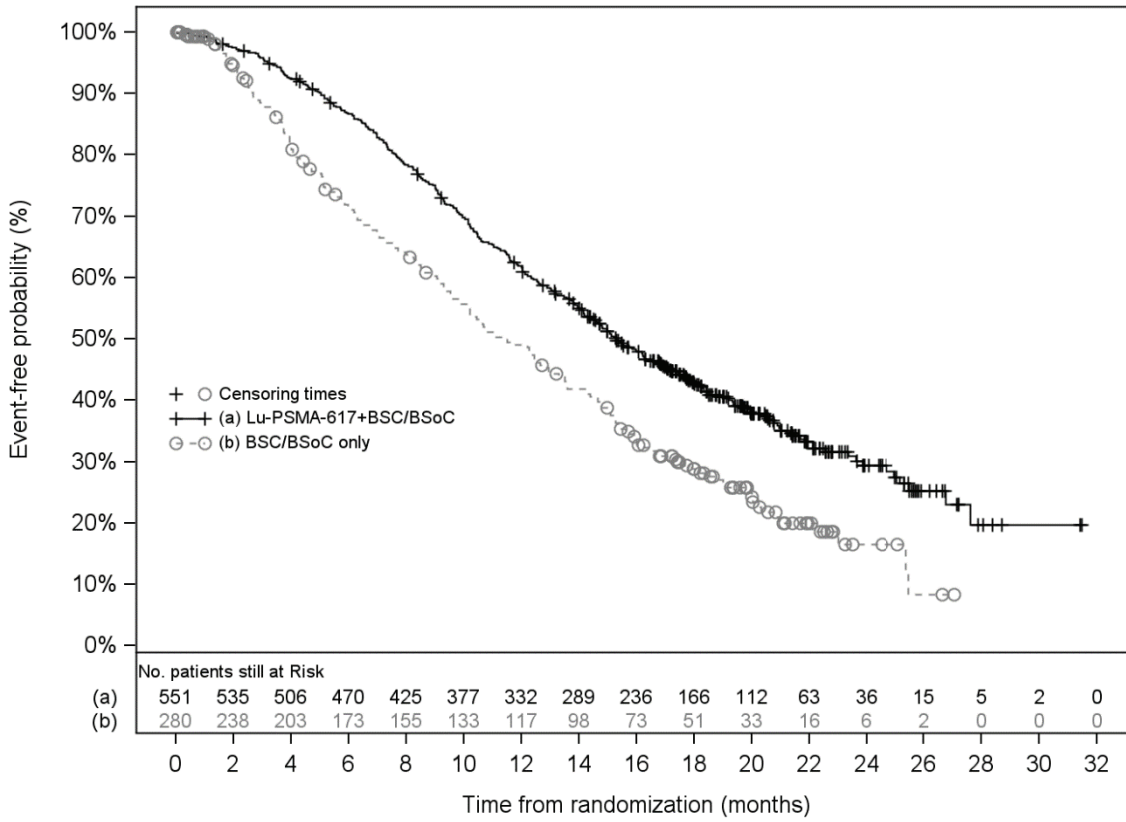
^a Based on Kaplan-Meier estimate.

^b Hazard ratio based on the stratified Cox PH model.

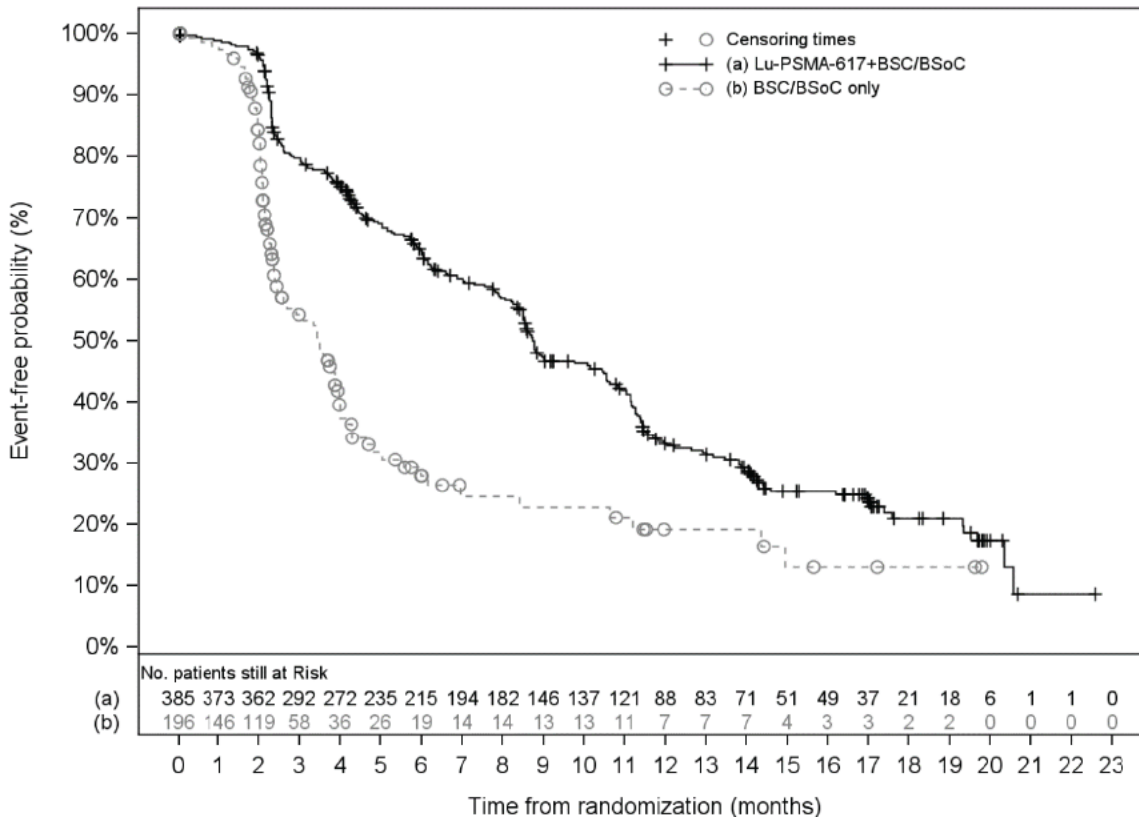
^c Stratified log-rank test two-sided p-value.

^d Stratified Wald's Chi-square test two-sided p-value.

Pluvicto: Kaplan-Meier Plot of Overall Survival in VISION



Pluvicto: Kaplan-Meier Plot of BICR-Assessed Radiographic Progression-Free Survival (rPFS) in VISION



Regarding the Applicant's position [redacted] (b) (4), the review team does not agree [redacted] (b) (4)

VISION Study of GOZ Reliability for Patient Selection

The Applicant's Position:

The reliability of GOZ PET scan reads supports use in identifying PSMA-positive lesions, based on the results of Study PSMA-617-01 Reviewer Variability Study, i.e. blinded independent reads of GOZ PET scans from Study PSMA-617-01 and supported by published literature.

Study PSMA-617-01 Reviewer Variability, included 125 patient scans, including 75 cases from enrolled patients (inclusion cases, randomly selected) and 50 cases from patients who were excluded from enrollment based on the Study PSMA-617-01 read criteria (exclusion cases, randomly selected). [redacted] (b) (4)

[redacted] The overall average agreement rate (P_{bar}) was 85% and the Fleiss' κ value was 0.60 (95% CI, 0.50-0.70), indicating moderate to substantial inter-reader agreement according to (Landis and Koch 1977), although the lower limit of the 95% CI (0.50) was slightly below the pre-defined threshold of 0.52. Factors potentially accounting for this were: study being conducted remotely, the high proportion of

exclusion cases in the sample, reader visual fatigue, and variability associated with different lesion types. The study results suggested that the visual assessment of GOZ PET/CT scan, using the read criteria, is robust and with a level of variability comparable to what has been reported in the literature. For intra-reader reproducibility, agreement rates ranged between 90-95% and Cohen's κ values of 0.78 (95% CI: 0.49-0.99), 0.76 (95% CI: 0.46-0.99), and 0.89 (95% CI: 0.67-0.99) were observed for each reader, demonstrating substantial to almost perfect agreement between repeated reads by the same reader. In a comparison of the read results from this reader variability study and those used to determine eligibility for Study PSMA-617-01, agreement rates ranging from 76% to 80% were observed for each reader, with better concordance among inclusion cases compared to exclusion cases for all three readers.

(b) (4)

Although the need to adapt the initially planned in-person training to a virtual setting due to the COVID-19 pandemic, as well as the increased proportion of the more challenging exclusion cases, likely led to slightly increased variability, these study results suggest that the visual assessment of GOZ PET/CT scans is robust.

The FDA's Assessment:

The review team agrees that the primary pre-specified result for the kappa study depended on how the lower bound of the 95% confidence interval (CI) for agreement between readers compared to the value of 0.52, a success criterion around the middle of the range (0.41 to 0.6) conventionally qualified as "moderate." The review team also agrees that the study result was found to be 0.6 and that the lower bound of the 95% CI was 0.5. Since 0.5 is less than 0.52, and the range between 0.5 to 0.6 falls into the range conventionally qualified as moderate, the review team disagrees with the position (b) (4)

The Applicant submitted a study report titled "Imaging Study Report: Reviewer Variability," including primary datasets, to the Locametz NDA. The review team performed further analysis of the submitted datasets in response to finding the kappa study had missed its pre-specified success criterion. This analysis aimed to address at least three issues. First, there was concern that the clinical meaningfulness of Fleiss' kappa may not be clear to many prescribers, in general, and in the context of evaluating efficacy for a new patient selection indication, in particular. Second, for the 125 subjects included in the kappa study, baseline GOZ PET imaging was interpreted by a total of four blinded, central readers. The reported endpoint, however, privileged the interpretation of some readers over that of others because the R0 reader was excluded from the analysis. This issue suggested analysis of agreement among all four readers might be informative. Finally, the positivity definition required readers to address four dichotomous questions and then to aggregate the set of answers into a final dichotomous response according to a set of conditional rules (for details, see Figure 3). One of the questions involved looking for any source of increased signal predominantly on PET imaging ("Any Lesion" criterion), while the other questions involved looking for decreased PET signal and required high levels of multi-modality correlation and attention to lesion-level detail ("All lesions $\geq$ Size" criteria). This difference suggested analysis based on eligibility sub-criteria might be informative.

Table 10 shows the results of reviewer analysis to address these issues.

Table 10. Reviewer Analysis of GOZ Imaging Interpretation in 125 Subjects With Multiple Reader Interpretations

Variable	Interpretation Criteria for Patient Selection					
	Any Lesion		All Lesions $\geq$ Size		Combined/Final	
Reader number (R)	4	3	4	3	4	3
Subject numbers (N,r,n)						
Interpretations ≥ 2 (N)	125	125	112*	109	125	125
Reader Agreement						
Fleiss' kappa (95% CI)	0.75 (0.68,0.82)	0.77 (0.67,0.87)	0.47 (0.39,0.55)	0.44 (0.33,0.54)	0.58 (0.51,0.65)	0.60 (0.50,0.70)
Did all readers agree (r) if any reader found criteria positive (n)?						
Consensus + % (r/n)	90 (104/116)	92 (106/115)	62 (65/108)	72 (76/105)	63 (66/105)	72 (76/105)
Did all readers agree (r) if any reader found criteria negative (n)?						
Consensus - % (r/n)	43 (9/21)	53 (10/19)	16 (7/45)	21 (7/34)	34 (20/59)	41 (20/49)

Source: Reviewer n1218 dataset traceable to Applicant-submitted primary sdtm data including under files ae, ex, lb, tr, tu, x5, x7, dm, ie, suppx5, x8, and suppx6.

*See also Section 8.1.1 for discussion of conditional CRF logic, including minor issue that required reconciliation for logic to be standardized with re-readers in rare cases where secondary negative criteria were recorded for the R0 reader.

Abbreviations: CI, confidence interval; GOZ, gozetotide; N, number of subjects; n, number of subjects within specific category; R, reader number

For interpretation of this table, the vertical bar symbol (|) denotes “given that.” For example, the row marked “Consensus|–” should be read as “consensus given negative.” This variable describes a fraction formed by the number of subjects for whom all readers provided a negative (ineligible) interpretation in the numerator, given that any reader provided a negative interpretation, reflected by the corresponding number of subjects in the denominator. As a complement to the pre-specified Fleiss kappa statistic, consensus adds an accessible concept of agreement. Comparing results in the table across the three criteria columns¹ shows a consistent pattern of variation, such that agreement is highest for the Any Lesion criterion, lowest for the All Lesions $\geq$ Size criteria, and intermediate for the Combined/Final (derivative) interpretation. These results, though post-hoc, align with the reasonable expectation that interpretive complexity undermines reader agreement. For the “All Lesions $\geq$ Size” criteria, the 95% CI lower bound for Fleiss' kappa and “Consensus|–” were only “fair” and 16%, respectively. For illustration, this result suggests that if a patient is found to be ineligible for Pluvicto because a reader finds a lesion larger than size criteria with GOZ uptake less than or equal to liver, at least one of another three second opinion readers might find the same patient eligible for Pluvicto up to 84% of the time ($0.84=1-0.16$).

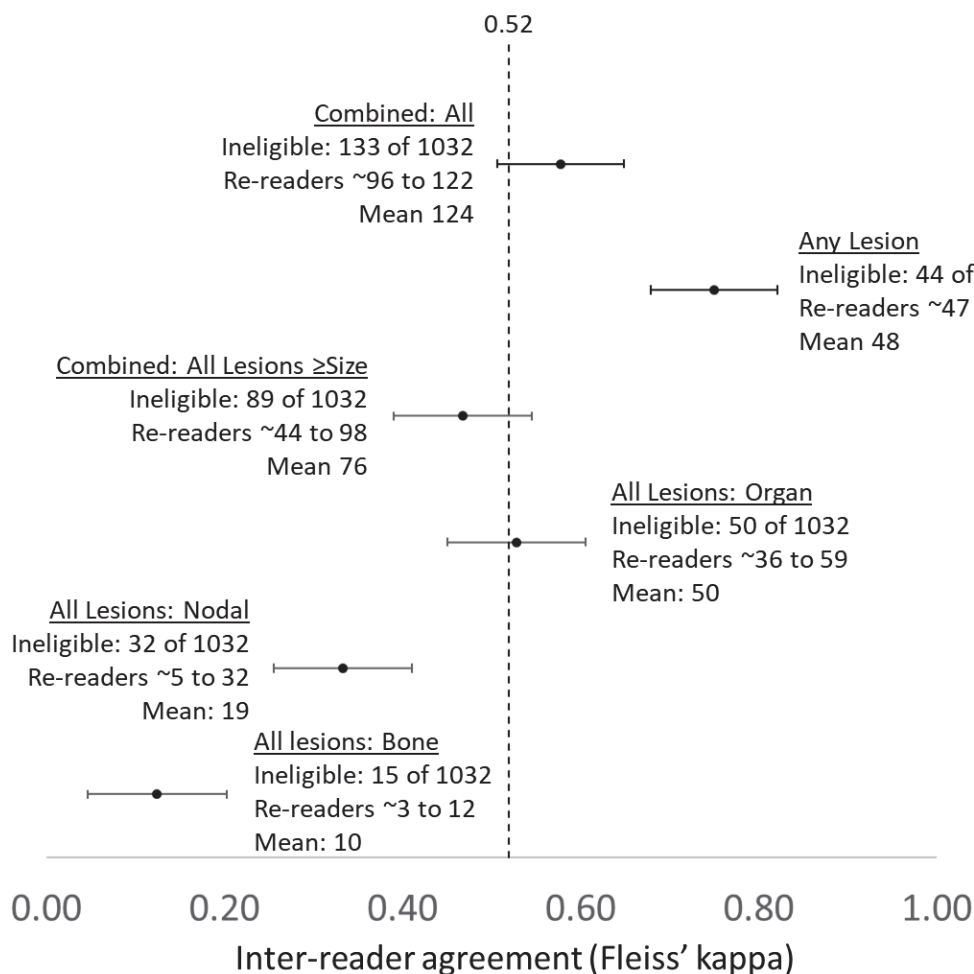
Variability involving the number and/or identity of patients selected for therapy can undermine reader agreement. In addition, from a theranostic imaging perspective, “ineligibility rate” (number of patients found ineligible for therapy as a percentage of the patients imaged for selection) represents a top-line result of the VISION trial and was found to be 13%². How did selection rate vary by reader based on the results of the kappa study? Recall from Section 8.1.1 that re-readers were not presented with imaging from all the subjects whose baseline imaging was first interpreted by the R0 reader (total positives: 899, total negatives: 133 negative); rather,

¹ The review team cautions the reader in drawing inferences from comparisons across rows in Table 10 because biological, imaging, and statistical factors all vary in this dimension and may confound interpretation.

² 13% = 26/995 or 133/1032, depending on whether or not the dosimetry cohort is counted, respectively.

sub-samples of 75 from among 899 and 50 from among 133, respectively, were randomly drawn and presented to the three re-readers. Leveraging these sampling proportions to weight re-reader's interpretations, ineligibility rate was compared across all readers, as shown in Figure 4.

Figure 4. Reviewer Analysis of GOZ Imaging Interpretations for Patient Selection From all Readers in the VISION Trial



Source: Reviewer n1218 dataset traceable to Applicant-submitted primary sdtm data including under files ae, ex, lb, tr, tu, x5, x7, dm, ie, suppx5, x8, and suppx6
 Note the horizontal axis represents Fleiss' kappa and varies from 0 to 1. The width of each horizontal bar corresponds to the 95%CI. Measured or derivative ("Combined") patient selection criteria are organized along the vertical axis. The dashed line is positioned at Fleiss' kappa of 0.52.
 Abbreviations: GOZ, gozetotide

Figure 4 provides annotations representing ineligibility rates in relation to patient selection criteria and also illustrates some of the same Fleiss' kappa results listed as in Table 10, with expansion to include granular analysis of the three "All Lesions ≥Size" sub-criteria (involving inspection of lesions in organ, nodal, and bone compartments). Weighting R0 and re-reader mean estimates equally, the combined ineligibility rate was 12% (=124/1032; range 9 to 14%). The All Lesions ≥ Size criteria contributed more to ineligibility than the Any Lesion criterion (7.3% vs 4.6%, respectively). Finally, the figure illustrates apparent dependence of the kappa statistic as ineligibility rate approaches zero, a relationship that may bear some conceptual similarity with

known hazards of overall accuracy in relation to prevalence as diagnostic metric of discrimination performance. For review of statistical issues, refer to Section 9.1.

Based on these sub-criteria results, under labeling Section 5 (“Warnings and Precautions”), prescribing information has revised to warn and mitigate the risk for misinterpretation specific to the issue of Locametz reader variability for patient selection:

The interpretation of LOCAMETZ PET may differ depending on imaging readers [*see Dosage and Administration (2.8)*]. LOCAMETZ PET interpretations to select patients for lutetium Lu 177 vipivotide tetraxetan therapy may be more consistent when judging gallium Ga 68 gozetotide uptake in any one tumor lesion compared to judging uptake for all lesions larger than size criteria [*see Clinical Studies (14.3)*]. Multidisciplinary consultation to select patients for lutetium Lu 177 vipivotide tetraxetan therapy is recommended, particularly for LOCAMETZ imaging that a single reader finds borderline or difficult to interpret, or when patient eligibility hinges only on judgment of gallium Ga 68 gozetotide uptake for all lesions larger than size criteria.

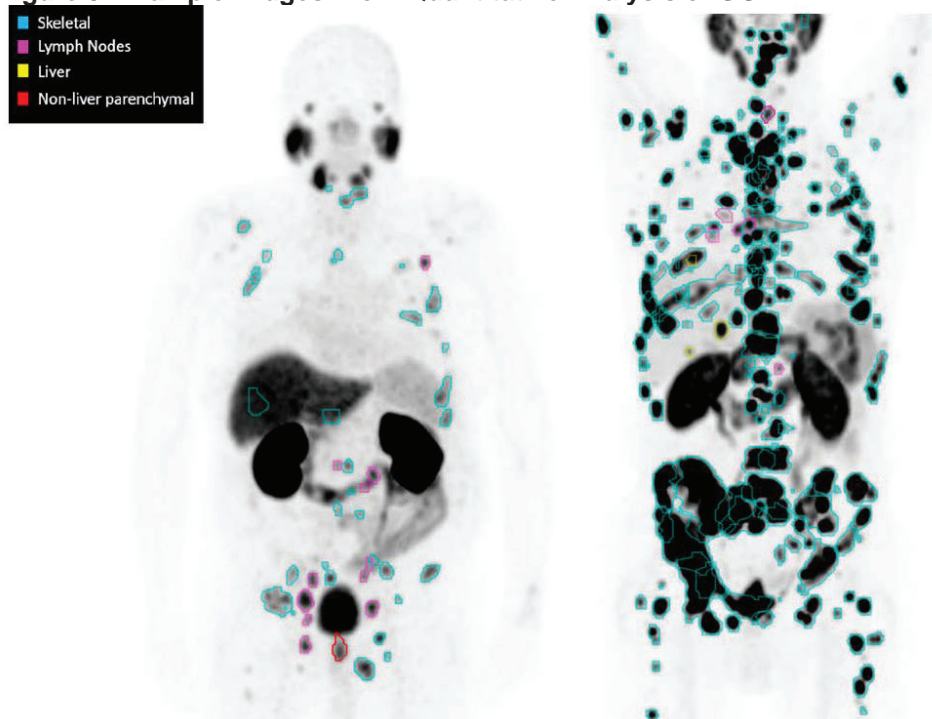
The labeling cross-reference to Clinical Studies (14.3) is bi-directional and also excerpted in the indented text below:

Given the observed levels of inter-reader agreement, patient’s PSMA interpretations were further evaluated by eligibility and eligibility sub-criteria. Of the 125 patients with four readers (reader and re-readers), at least one reader found the patient to be PSMA-negative for lutetium Lu 177 vipivotide tetraxetan therapy in 59 patients. All four readers agreed in 20 of the 59 patients (34% reader unanimity). Based on the sub-criteria involving evaluation of any one tumor lesion and evaluation of all lesions larger than size criteria, at least one reader found the patient to be PSMA-negative in 21 patients (43% reader unanimity) and 45 patients (16% reader unanimity), respectively [*see Warnings and Precautions (5.1)*].

VISION Study Exploring Imaging and Outcomes

The Applicant submitted a study report to the Locametz NDA titled “Imaging Study Report: Quantitative Analysis.” Quantitative analysis of baseline GOZ PET was completed for 548 of the 551 subjects randomized to Pluvicto in the VISION trial. For example images from two of these subjects, see Figure 5.

Figure 5. Example Images From Quantitative Analysis of GOZ PET



Source: NDA215841\0016\m1\us\fdareponse-clinical.pdf.

Note images are displayed in anterior maximum intensity projection (MIP) views. Tumor lesion outlines are superimposed and color-coded by anatomical classification (see key). A total of 43 lesions were outlined for the subject on the left. Readers disagreed on patient selection for this subject. A total of 176 lesions were outlined for the subject on the right. All readers agreed that this subject was positive (eligible). Per protocol, imaging was acquired with subjects supine and arms above the head unless unable. Abbreviations: GOZ, gozetotide; PET, positron emission tomography

The figure illustrates the widespread and large number of lesions identified per subject and characteristic of the advanced spectrum of disease studied in the VISION trial.

Table 11 provides a descriptive summary of the quantitative imaging results.

Table 11. GOZ SUV and Lesion Volume in Subjects Randomized to Pluvicto

Compartment	Number (%) of subjects with one or more tumor lesions	Total Volume (cc) Mean Median Range (min, max)	SUV_{mean} Mean Median Range (min, max)	SUV_{max} Mean Median Range (min, max)
Bone	508 (93)	684	7.3	35
		289	6.6	28
		(0.1,4919)	(1.7,53)	(2.1,317)
Lymph node	369 (67)	152	8.8	32
		46	7.7	23
		(0.4,3103)	(1.8,53)	(2.3,208)
Soft tissue	233 (43)	75	8.9	23
		14	7.6	17
		(0.3,3886)	(1.4,36)	(1.9,167)
Liver	72 (13)	280	8.6	20
		43	8.2	16
		(0.6,3761)	(2.0,33)	(2.3,73)
All (whole body)	548 (100)	805	8.4	42
		398	7.5	34
		(1.7,5370)	(1.6,38)	(2.0,317)

Source: Reviewer analysis of NDA 215841\0008\m5\datasets\psma-617-01\tabulations\sdtm\x7.xpt
 Abbreviations: GOZ, gozetotide; SUV, standardized uptake value

The table shows that bone (93%) and lymph node (67%) were the anatomical compartments where disease was detected most commonly, assuming lesions detected by the Applicant’s semi-automated analysis all represent correctly classified metastases. Notably, the marked difference between mean and median estimates for total volume reflects a non-normal distribution skewed to the right, including subjects identified as having lesions with GOZ uptake potentially totaling up to 5 liters of disease. To help put GOZ SUV in some context, the Applicant estimated that the normal liver SUV for GOZ in this dataset ranged between 1 and 10.

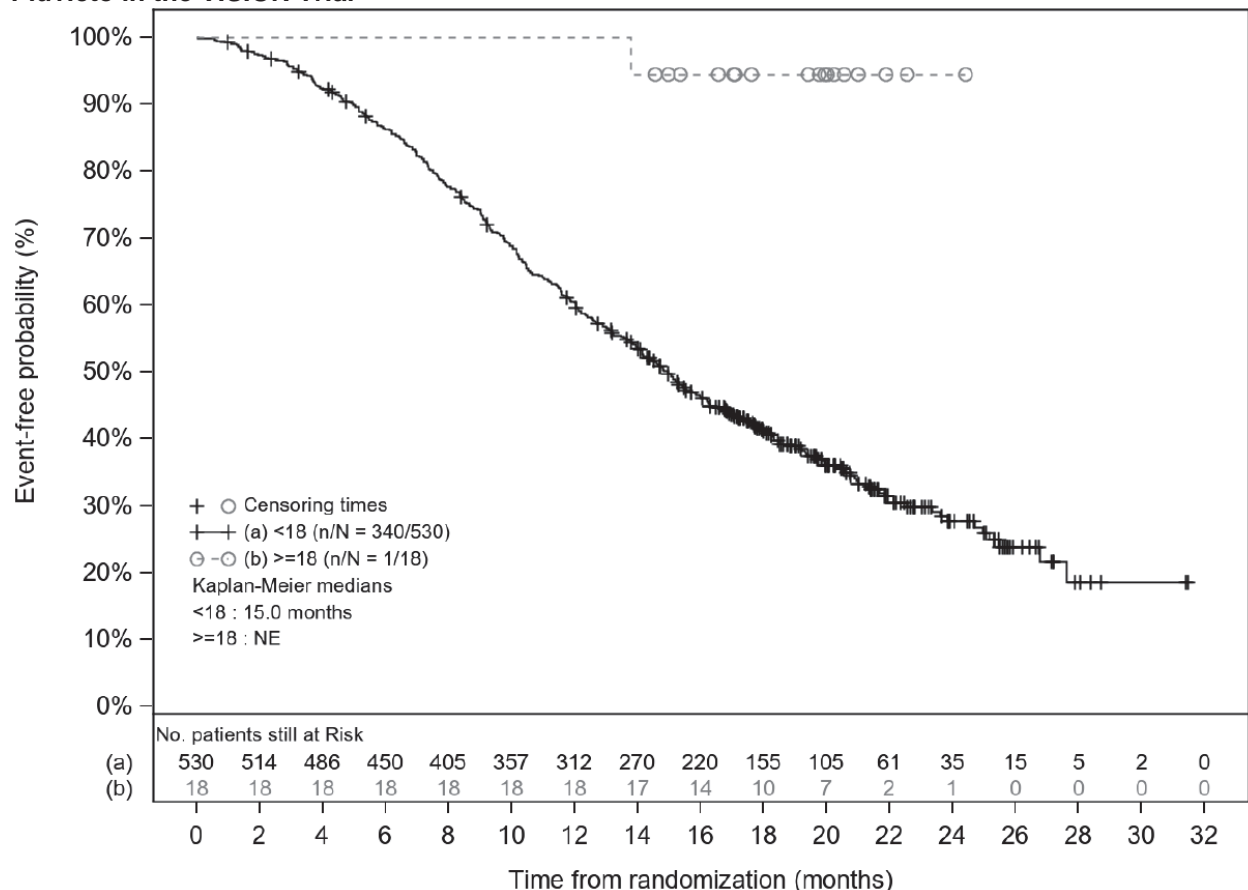
Study results consisted primarily of parameter outputs following pre-specified exploratory statistical modeling. Refer to Section 9.1 for statistical review. Conceptually, limited to the group of subjects randomized to the VISION trial investigational arm, subject-to-subject variance for the imaging measures summarized in Table 11 was modeled as independent, with the aim of accounting for subject-to-subject variance in trial outcomes modeled as dependent (refer to FDA’s separate multi-disciplinary review and evaluation for Pluvicto for review of trial outcomes directly linked to therapy). Broadly speaking, the Applicant interpreted these modelling results as showing that measures of increased PET activity, in general, and whole body GOZ SUV_{mean}, in particular, were associated with improved clinical outcomes following VIP therapy.

The Applicant’s report also included results of an exploratory cutpoint analysis. The aim was to find optimal cutpoints for distinguishing patient subgroups in terms of outcomes. For example, what value of whole body SUV_{mean} best distinguished one subgroup with more positive GOZ activity on baseline PET (positive++) from another subgroup with less positive GOZ activity on baseline PET (positive+)³, such that the difference in OS between positive++ and positive+ subgroups would be maximized? To address this question, the Applicant tried varying candidate

³ Recall that GOZ-negative subjects were ineligible for randomization, so not included in the quantitative analysis dataset consisting of subjects randomized to the investigational arms.

whole body SUV_{mean} cutpoints in increments of 1 (from <7 to <18), seeking the value that maximally separated the area under the Kaplan-Meier survival curves between the varying positive++ and positive+ subgroups. Figure 6 illustrates the reported optimal result (cutpoint=18).

Figure 6. OS in Subjects With Baseline GOZ $SUV_{mean} \geq 18$ vs $SUV_{mean} < 18$ Following Randomization to Pluvicto in the VISION Trial



Source: The Applicant's submission under NDA215841\0008\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\pc\5351-stud-rep-contr\psma-617-01\psma-617-01--imaging-quantitative-analysis.pdf.
 Note that for each group, n/N refers to the number of deaths/number of subjects corresponding to 100% on the y-axis, respectively
 Abbreviations: GOZ, gozetotide; NE, not examined; OS, overall survival; SUV_{mean} , mean standardized uptake value

The figure shows that median OS was estimated to be 15 months for subjects in the $SUV_{mean} < 18$ subgroup (positive+, N=530) compared to not yet reached in the $SUV_{mean} \geq 18$ subgroup (positive++, N=18, with follow-up ranging between ~15 to ~25 months). Though the separation between curves in the figure is visually striking, the review team also identified some issues with this analysis. First, application of the method in this theranostic context seems biased toward identifying extreme cutpoints and may not be fit for purpose. Second, using $SUV_{mean} \geq 18$ (or re-designing qualitative selection criteria to target a similarly extreme positive++ subgroup) could imply that eligibility for Pluvicto should be limited only to a tiny subset of the investigational arm that was found as a whole to benefit in the VISION trial. In short, the clinical relevance of the Applicant's cutpoint analysis is unclear.

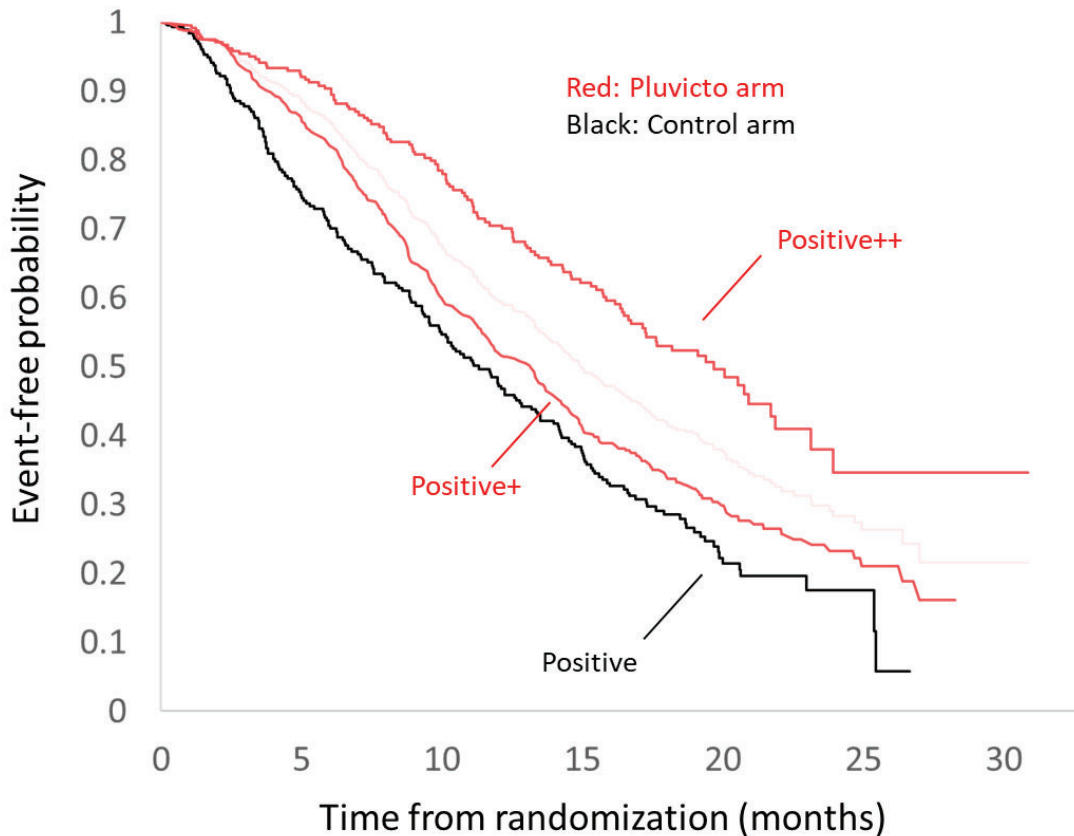
To address this issue, the review team conducted another exploratory cutpoint analysis starting from the position that, in the context of the VISION trial, it would be clinically relevant to predict whether subjects randomized to VIP survive longer than subjects randomized to the

control arm. Comparing OS results from the trial across the two arms, Kaplan-Meier median OS was found to be 15.3 vs. 11.3 months in favor of Pluvicto. Using 13.2 as the estimate (univariate) for the upper bound of the 95%CI for the control arm, the team sought to determine the cutpoint for GOZ SUV that best predicted whether subjects randomized to Lu177-PSMA survived longer than 13.2 months (i.e., longer than likely without Pluvicto). An analysis was conducted, counting subjects surviving ≥ 13.2 months as true|false (314|234) and subjects with $SUV_{mean} \geq$ cutpoint as positive|negative (i.e., positive++|positive+). Accordingly, 2x2 truth tables could then be tried across the range of measured SUV_{means} . At the cutpoint of 8.9, the number of true positive (TP) and true negative (TN) subjects was 126 and 171, corresponding to maximum combined sensitivity (Sn) and specificity (Sp) estimates of 0.4 and 0.73, respectively (ROC AUC = 0.6)⁴. Though post-hoc and exploratory, these performance estimates provide hypothesis generating evidence to suggest that GOZ SUV_{mean} cutpoints in a clinically reasonable range may have better-than-chance performance for predicting clinically relevant OS in patients treated with Pluvicto.

This analysis also suggested that compared to $SUV_{mean} \geq 18$, $SUV_{mean} \geq 8.9$ is a more clinically relevant cutpoint for comparison of OS between positive+ and positive++ subgroups. Figure 7 shows these results.

⁴ For comparison, Sn and Sp performance was at chance using the SUV_{mean} cutpoint of 18.

Figure 7. Reviewer's Analysis of OS in Subjects With Baseline GOZ $SUV_{mean} \geq 8.9$ Versus $SUV_{mean} < 8.9$ Following Randomization to Pluvicto in the VISION Trial



Source: Reviewer n1218 dataset traceable to Applicant-submitted primary sdtm data including under files ae, ex, lb, tr, tu, x5, x7, dm, i.e., suppx5, x8, and suppx6.

Note: The faint red and black lines show the proportion of subjects surviving in the VISION trial among the 551 and 280 randomized to investigational and control arms, respectively. From among the 551, the solid red lines show the proportion of subjects surviving among the 189 and 359 with quantitative imaging data and $SUV_{mean} \geq 8.9$ (positive++ subgroup) and $SUV_{mean} < 8.9$ (positive+ subgroup), respectively. In order from the top-most line down, median survival (95%CI) in months was estimated via reviewer (non-stratified) Kaplan Meier analysis to be 19.7 (16.6,21.9), 14.9 (13.8,16.5), 13.2 (11.4,14.3), and 11.3 (9.5,13.2) months, respectively. Abbreviations: GOZ, gozetotide; OS, overall survival; SUV_{mean} , mean standardized uptake value

The figure shows a clear subgroup effect for OS (separation between solid red lines) superimposed on the primary arm-level group effect of the VISION trial (separation between faint red and solid black lines). In particular, the separation between interventional and control arms is more pronounced for the GOZ positive++ subgroup (N=189) and diminished (though still directionally favorable) for the positive+ (N=359) subgroup. Refer to Section 2 for discussion of published evidence favoring the hypothesis that the uninvestigated separation between positive++ and positive+ subgroups in the control arm (black line) will be in the opposite direction (i.e., survival positive+ > positive++).

In summary, if the exploratory analyses performed by the Applicant and review team can be confirmed and are specific to selected patients, it would suggest that patient selection criteria based on GOZ activity of increased magnitude (e.g., Any Lesion criteria) and widespread body

distribution (e.g. All Lesions $\geq$ Size criteria) represent effective dimensions along which to select patients for VIP therapy.⁵

To test whether these quantitative imaging analysis results were specific to selected subjects, the Applicant has agreed to the following postmarket study commitment (PMC) and timeline:

- Perform an expanded imaging analysis to include the VISION trial control arm for the study titled Imaging Study Report: Quantitative Analysis. The final report should be submitted in clean and marked versions to highlight the control-arm results added in comparison to the originally submitted study report.

Final Protocol Submission: 03/2022

Final Report Submission: 10/2022

See also FDA’s Multi-disciplinary Review and Evaluation for Pluvicto regarding planned PMC for patients with advanced/metastatic PC who had at least one PSMA-expressing tumor but did not meet the selection criteria used in VISION.

VISION Study of Dosimetry

Radiation absorbed dose (AD) estimates for GOZ and VIP are presented in Table 12 below.

Table 12. Radiation Absorbed Dose Estimates for GOZ and VIP

Region	GOZ, N=13 (mGy/MBq=Gy/GBq)		VIP, N=29 (mGy/MBq=Gy/GBq)	
	Mean	SD	Mean	SD
Adrenals	0.0156	0.0014	0.033	0.025
Brain	0.0104	0.0011	0.007	0.005
Breasts	0.0103	0.0011	N/A	N/A
Esophagus	N/A	N/A	0.025	0.026
Eyes	N/A	N/A	0.022	0.024
Gallbladder wall	0.0157	0.0012	0.028	0.026
Heart wall	0.012	0.0009	0.17	0.12
Kidneys*	0.3714	0.0922	0.43	0.16
Lacrimal glands	N/A	N/A	2.1	0.47
Left colon	N/A	N/A	0.58	0.14
Liver*	0.0409	0.0076	0.09	0.044
Lungs	0.0111	0.0007	0.11	0.11
Muscle	0.0103	0.0003	N/A	N/A
Pancreas	0.0147	0.0009	0.027	0.026
Prostate	N/A	N/A	0.027	0.026
Rectum	N/A	N/A	0.56	0.14
Red marrow	0.0114	0.0016	0.035	0.02
Right colon	0.0134	0.0009	0.32	0.078
Salivary glands	N/A	N/A	0.63	0.36
Skin	0.0091	0.0003	N/A	N/A
Small intestine*	0.014	0.002	0.071	0.031

⁵ Comparison of imaging and outcome data from selected and unselected patients are lacking and would be more fit for purpose to support any claim that selection criteria are optimal or near-optimal.

Region	GOZ, N=13 (mGy/MBq=Gy/GBq)		VIP, N=29 (mGy/MBq=Gy/GBq)	
	Mean	SD	Mean	SD
Spleen*	0.065	0.018	0.067	0.027
Stomach wall	0.0129	0.0008	0.025	0.026
Testes	0.0111	0.0006	0.023	0.025
Thymus	0.0105	0.0006	0.025	0.026
Thyroid	0.0104	0.0006	0.26	0.37
Total body	0.0143	0.0013	0.037	0.027
Urinary bladder wall*	0.0982	0.0286	0.32	0.025
Effective dose (mSv/MBq)	0.0169	0.0015	N/A	N/A

Source: NDA215841\0000\m5\53-clin-stud-rep\535-rep-ffic-safety-stud\pc\5351-stud-rep-contr\psma-617-01\psma-617-01--vital-signs.pdf

Note that for GOZ, dosimetry relies on the PI for the LD, as excerpted here per reviewer matching. The results shown for VIP rely on first cycle data from the Applicant's dosimetry study (N=29). *Regions measured with ROI/VOLs for both GOZ and VIP.

Abbreviations: GOZ, Ga68-gozetotide; N, number of subjects; VIP, Lu177-vipivotide tetraxetan

For VIP, organs estimated to receive the highest AD (standard deviation, SD) were lacrimal (2.1 (0.47) Gy/GBq) and salivary (0.63 (0.36) Gy/GBq). For the recommended administered activity (AA) per cycle and number of cycles (7.4 GBq × 6 = 44.4 GBq cumulative AA), estimated cumulative AD was 92 (21) Gy and 28 (16) Gy, respectively. Estimated cumulative dose to the kidneys was 19 (7.3) Gy. Note that in relation to thresholds used for planning delivery of conventionally fractionated external beam radiation therapy (XRT), where off-target exposure greater than 25 to 30 Gy for lacrimal/salivary glands and 18 to 23 Gy for kidneys is typically avoided, cumulative AD in the VISION dosimetry study was found to exceed these points of reference for multiple subjects. Refer to the FDA's Multi-disciplinary Review and Evaluation of safety for Pluvicto, including adverse reaction rates for dry mouth (39%; all Grade ≤ 2), dry eye (<5%), and acute kidney injury (Grades All|3 to 4 of 9%|3.2%, compared to 6%|2.9% in the control arm). In general, without accounting for differences involving metrology, pharmacology, radiation biology, clinical context, and product regulation, the review team cautions the reader in applying experience with the use of AD in XRT to assess the safety of new therapeutic radiopharmaceuticals.

The team identified an additional review issue involving the row labeled "Red Marrow" in Table 12. In particular, the Applicant's method for estimating AD to the hematopoietic system neglected to account for the contribution of irradiation sources seen on imaging. Rather, in terms of clinical measurement inputs, the Applicant relied solely on counts detected in vitro from blood sampling. This methodological issue would be expected to lead to underestimation of AD (i.e., true hematopoietic AD higher than measured). Indeed, the measured AD estimate of 0.035 (0.02) Gy/GBq amounts to 0.259 (0.15) Gy per administration cycle⁶, well short of typically myelosuppressive ADs ≥ ~2 Gy. The Applicant's dosimetry report acknowledged that for patients with disease where cross-fire from tumor to hematopoietic tissue may be an issue, AD to the red marrow may not be "well characterized by the dosimetric model employed in this analysis." The review team agreed that this disclaimer applied to the VISION trial population (see Figure 5) and invited the Applicant to re-analyze the dataset accounting for imaged sources

⁶ For risk of myelosuppression, AD per cycle is more relevant than cumulative AD because a primary rationale for cycling is to leverage rapid physiological turnover in the hematopoietic system and allow time for recovery from myelosuppression.

of irradiation to the hematopoietic system. The Applicant declined, so the issue was addressed via labeling revision, as described in the indented excerpt from the prescribing information for Pluvicto:

Under Table titled “Estimated Radiation Absorbed Dose for PLUVICTO in VISION:
*Estimated radiation absorbed dose for bone marrow is not included [see Warnings and Precautions (5.2)].

Warning and Precaution 5.2 (“Myelosuppression”): PLUVICTO 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 PLUVICTO. Grade ≥ 3 pancytopenia occurred in 1.1% (which includes two fatal events) in patients treated with PLUVICTO. Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia were observed in patients who received PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on the severity of myelosuppression [see Dosage and Administration (2.4)].

For additional discussion of mainly null findings involving hematopoietic dosimetry/toxicity analysis, refer to the pharmacometrics portion of FDA’s Multi-disciplinary Review and Evaluation for Pluvicto.

Turning from VIP to GOZ dosimetry, the review team conducted an exploratory analysis of the level of association between the two. Starting from the assumption that the ideal imaging radiopharmaceutical to select patients for a theranostic pair would have identical biodistribution (not identical ADs), the team reasoned that evidence of similarity in region-to-region variation between GOZ and VIP could provide additional support relevant to efficacy. A linear analysis of region-to-region AD variance was thus performed for the region-matched data listed in Table 12. For the ADs derived from direct measure (i.e. from imaging ROI/VOIs, 5 regions), r^2 was found to be 0.86. For comparison, from an equivalent analysis involving GOZ and the Lu177-DOTATATE PI, r^2 was found to be 0.57. Though limited by multiple sources of uncertainty (including cross-study comparisons, clinical relevance of differences in biodistribution, etc.), these exploratory findings are directionally supportive of GOZ for patient selection. In addition, this direction of analysis may point toward the potential to leverage dosimetry data for new investigational aims involving theranostic development.

8.1.3. Assessment of Efficacy Across Trials

This section is not applicable to this NDA.

8.1.4. Integrated Assessment of Effectiveness

In responding to sponsor questions about radiopharmaceutical co-development for new patient selection indications, FDA review teams have focused on the following considerations:

- Will evidence be substantial that the selected therapy provides favorable benefit-risk after patient selection?
- Will investigation of imaging interpretation be adequate and well controlled to establish the reliability of the selection criteria described in prescribing information?
- Will subgroup analysis be pre-specified to support favorable outcomes in selected versus ineligible patients or, if unavailable, in positive++ versus positive+ subgroups?
- Will clinical pharmacology and dosimetry data support overlap in biodistribution between imaging and therapeutic agents?

In this NDA, the Applicant has provided generally affirmative evidence to address these questions. In particular:

- The Pluvicto review team found that evidence from the VISION trial was substantial. After patient selection with GOZ in adult patients with mCRPC who had been treated with androgen receptor pathway inhibition and taxane-based chemotherapy, Pluvicto improved survival. The therapy was considered relatively well tolerated, with favorable benefit-risk.
- The VISION study of GOZ reliability for patient selection was adequate and well controlled. It showed that Fleiss' kappa, but not the lower bound of the 95%CI, exceeded the pre-specified threshold of 0.52. The Applicant has agreed to labeling changes to highlight and mitigate certain likely root causes of this limited performance in the selection criteria. Accounting for these changes, the review team finds Locametz reliability is adequate to select patients for VIP therapy.
- The VISION study exploring imaging and outcomes showed separations in OS favoring positive++ over positive+ investigational arm subgroups, with the magnitude of separation numerically exceeding the OS advantage of the interventional arm over the control arm. The magnitude of this exploratory result thus appears large, suggesting that accounting for both lesion-level GOZ activity and lesion-to-lesion uniformity throughout the body is an effective strategy for patient selection. This strategy is reflected in the Locametz selection criteria. The exploratory result nevertheless lacks confirmation; evidence of specificity to VIP is also lacking. The Applicant has agreed to a PMC that may address these limitations.
- Finally, limited exploratory analysis of available dosimetry data supports overlap in biodistribution between GOZ and VIP.

In summary, the review team finds that there is substantial evidence from the VISION trial plus confirmatory evidence from VISION studies to establish that Locametz is effective to select patients with metastatic PC for whom VIP PSMA-directed therapy is indicated.

Note that efficacy has not been established for use of Locametz to select patients for all PSMA-targeted therapy (i.e., any combination of radionuclide and small molecule or biologic that targets PSMA), since no other PSMA-directed therapy was investigated. In addition, the safety and efficacy of using Locametz as prescribed to select patients for VIP may be different if used to select patients for other PSMA-directed therapies.

8.2. Review of Safety

The Applicant's Position:

The primary source of safety data for GOZ is Study PSMA-617-01, the largest source of prospectively collected safety data for the compound as all patients were administered GOZ to determine patient eligibility based on PET imaging patterns defined by the central read criteria. In Study PSMA-617-01, the PSMA-11 safety analysis set included all patients who received a dose of ⁶⁸Ga-PSMA-11. The safety population comprises 1003 patients with mCRPC.

Five publications were identified to provide supportive safety data for GOZ: (Fendler et al. 2019) in 635 patients, (Nielsen et al. 2017) in 88 patients, (Afshar-Oromieh et al. 2017) in 1007 patients, (Caroli et al. 2018) in 314 patients, and (von Eyben et al. 2018) in 1256 patients. There is some overlap in patients included in meta-analysis by (von Eyben et al. 2018) and the retrospective analysis (Afshar-Oromieh et al. 2017). Together, these 5 articles report the safety of GOZ in over 3000 patients.

In the GOZ applications recently approved by FDA, safety was evaluated in 960 patients, each receiving one dose of Gallium Ga 68 PSMA-11 Injection (Gallium 2020a; Gallium 2020b). There is partial overlap in patients included in (Fendler et al. 2019) and the UCLA contribution to the FDA-approved dossier (specifically, trial NCT02940262).

Based on the extensive data reviewed on the use of GOZ in patients with prostate cancer, this is considered adequate to assess the safety profile in this patient population. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

FDA agrees with the Applicant that the primary source of safety data for GOZ is VISION study. Another source for the safety review is FDA's findings of safety of the LD.

8.2.1. Safety Review Approach

The Applicant's Position:

Within Study PSMA-617-01 the treatment-emergent period was defined as the period from the date of GOZ dosing up to 6 days after the date of ⁶⁸Ga-PSMA-11 dosing as long as this was prior to Cycle 1 Day 1 (CID1). AEs reported as "possibly," "probably," or "definitely" related to GOZ that occurred beyond the 6-day reporting window but occurred before the date of initiation of randomized treatment (CID1) were also considered as GOZ AEs. Unrelated AEs that occurred beyond 6 days were not considered GOZ AEs. Since patients could start BSC/BSoC before randomization, some patients might have received BSC/BSoC before or shortly after GOZ administration. Thus, AEs reported as "possibly," "probably," or "definitely" related to GOZ could instead be related to either GOZ or BSC/BSoC. Therefore, the GOZ safety profile may also include BSC/BSoC-related events. For the SAEs and deaths, the distinction between GOZ -related events and BSC/BSoC-related events was drawn from the pharmacovigilance database.

AEs and SAEs were assessed together with their CTCAE grade and relationship to study drug. Of note, the GOZ PET/CT scan was done only once, and, therefore, no AEs leading to discontinuation were collected.

Analyses also included safety topics of interest, selected based on routine risk assessments and/or biological plausibility. MedDRA version 23.1 and CTCAE version 5.0 was used for coding AEs. Laboratory evaluations, vital signs, and ECG measurements were not specifically assessed post-dose for GOZ.

Supportive literature (5 publications) was reviewed for AE reporting. None of the literature sources reported on laboratory safety assessments. One publication (Nielsen et al. 2017) included limited information on vital sign assessments.

In the studies used for FDA approval of GOZ, patients were monitored for adverse events for 2 hours after drug injection and by phone call at 1 to 3 days after injection ([FDA 2020a](#), [FDA 2020b](#)).

The FDA's Assessment:

FDA agrees with the Applicant's safety review approach.

8.2.2. Review of the Safety Database

Overall Exposure in Study PSMA-617-01; PMSA-11 Safety Set

In Study PSMA-617-01, GOZ was administered intravenously at a planned dose of 111-185 MBq (3-5 mCi) (b) (4). The actual dose administered to patients, with a corresponding body weight adjusted dose range is outlined in Table 13. Overall, 149 of 1003 patients received activity injected-decay corrected dose exceeding 5 mCi (> 185 MBq) with a mean dose of 2.3 MBq/kg in Study PSMA617-01.

Table 13. ⁶⁸Ga-PSMA-11 Exposure (Study PSMA-617-01, PSMA-11 Safety Analysis Set)

Variable	Overall N=1003
⁶⁸ Ga-PSMA-11 activity injected-decay corrected dose (MBq)*	
n	1003
Mean (SD)	167.1 (23.1)
Median	166.6
Min-Max	92.8-287.5
⁶⁸ Ga-PSMA-11 activity injected-decay corrected* dose per body weight (MBq/kg)	
n	976
Mean (SD)	2.0 (0.4)
Median	1.9
Min-Max	0.9-3.7

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

*A decay correction calculation was performed if there was more than 3 minutes between pre-injection syringe measurement time and ⁶⁸Ga-PSMA-11 administration time or if there was more than 3 minutes between post-injection syringe measurement time and ⁶⁸Ga-PSMA-11 administration time.

Abbreviations: N, number of subjects; PSMA, prostate-specific membrane antigen

Supportive Literature

Across the 5 articles, > 3000 patients were exposed to single-dose GOZ during PET imaging and mean total dose/radiation activity across the studies ranged from 150 to 227 MBq (4.05 to 6.14 mCi), with imaging acquisition performed approximately 60 minutes following GOZ administration.

⁶⁸Ga-PSMA-11 Approved by FDA

For the recently FDA-approved Gallium Ga 68 PSMA-11 Injection, the safety was evaluated in 960 patients, each receiving one dose of Gallium Ga 68 PSMA-11 Injection. The mean (SD) injected activity was 188.7 (40.7) MBq, i.e. 5.1 (1.1) mCi (Gallium Ga 68 PSMA-11 USPI 2020a, Gallium Ga 68 PSMA-11 USPI 2020b). The radiation absorbed dose per Dosimetry USPI associated with an injected radioactivity of 5 mCi resulted in an effective whole-body dose of approximately 3.1 mSv (FDA 2020a, FDA 2020b).

The FDA's Assessment:

FDA agrees with the Applicant's overall exposure in VISION and LD studies.

Relevant Characteristics of the Safety Population:

The Applicant's Position:

Demographics and disease characteristics are as expected in this population of patients with progressive PSMA-positive mCRPC (Table 14).

Table 14. Demographics and Disease Characteristics (Study PSMA-617-01, PSMA-11 Safety Analysis Set)

Variable	Overall N=1003
Age (years)	
n	1003
Mean (SD)	69.9 (7.6)
Median	70.0
Min-Max	40-94
Age (categorized), n (%)	
<65 years	251 (25.0)
≥65 years	752 (75.0)
≥65-84 years	733 (73.1)
≥85 years	19 (1.9)
Race, n (%)	
White	868 (86.5)
Black or African American	66 (6.6)
Asian	24 (2.4)
Other ¹	4 (0.4)
Missing	41 (4.1)
Ethnicity, n (%)	
Hispanic or Latino	18 (1.8)
Not Hispanic or Latino	858 (85.5)
Not reported	127 (12.7)

Variable	Overall N=1003
Weight (kg)	
n	938
Mean (SD)	88.4 (17.3)
Median	86.0
Min-Max	53.4-171.9
Body Mass Index (kg/m ²)	
n	907
Mean (SD)	28.4 (5.1)
Median	27.73
Min-Max	17.0-57.4
Time since initial cancer diagnosis (years)	
n	1003
Mean (SD)	8.3 (5.5)
Median	7.0
Min-Max	0.3-28.9
Initial histopathological classification, n (%)	
Adenocarcinoma	908 (90.5)
Neuroendocrine	1 (0.1)
Unknown	85 (8.5)
Other	9 (0.9)

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

¹ Other includes Native Hawaiian or other Pacific Islander and American Indian or Alaska Native and more than one race reported.

Abbreviations: N, number of subjects; n, number of subjects within specific category; PSMA, prostate-specific membrane antigen

The FDA's Assessment:

FDA agrees with the Applicant's assessment of demographics and disease characteristics in VISION.

Adequacy of the Safety Database

The Applicant's Position:

The primary source of safety data for GOZ is Study PSMA-617-01 in which 1003 patients with mCRPC underwent a GOZ PET/computed tomography (CT) scan. Safety information from the FDA-approved Gallium Ga 68 PSMA-11 Injection and from relevant literature provide additional support. These sources are considered adequate to assess the safety profile in adult patients with prostate cancer.

The FDA's Assessment:

FDA agrees with the Applicant that the above listed sources are considered adequate to assess the safety profile in adult patients with prostate cancer.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

Regarding Study PMSA-617-01, PMSA-11 safety set, 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; data in the CRFs and adverse event databases were consistent.

The FDA's Assessment:

No issues regarding data integrity and submission quality were identified by FDA review team.

Categorization of Adverse Event

The Applicant's Position:

Adverse events were evaluated for the following categories:

- *Frequency, type (by SOC and PT), severity, and causal relationship of AEs to study drug*
- *Deaths, frequency of SAEs*

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

The FDA's Assessment:

FDA agrees with the Applicant's categorization of AEs.

Routine Clinical Tests

The Applicant's Position:

Laboratory evaluations, vital signs, and ECG measurements were not routinely assessed in the days immediately following ⁶⁸Ga-PSMA-11 administration until day 1 of cycle 1 of subsequent randomized treatment.

The FDA's Assessment:

The day 1 of cycle 1 of subsequent randomized treatment is at least 14 days after administration of GOZ. Therefore, the laboratory evaluations, vital signs, and ECG measurements at that time will not be applicable to safety evaluation of GOZ.

8.2.4. Safety Results

The Applicant's Position:

Deaths

During the AE window between GOZ dosing and 6 days after, 3 patients (0.3%) had a SAE leading to fatal outcome. The investigator did not attribute any of these fatal events to the study or the study drugs including GOZ, but rather to the patients' underlying advanced disease.

- *The fatal SAE of cardiorespiratory arrest was reported for a 72-year-old male patient; the cause of death recorded on the death certificate was cardiopulmonary arrest secondary to complications due to prostate cancer. The patient was known to have had a pulmonary embolism previously.*

- *The fatal SAE of subdural hematoma was reported for a 64-year-old male patient who was hospitalized after being found unresponsive at home and died despite intensive care. A CT scan of the head showed massive right holocephalic subdural hematoma and significant subfalcine herniation.*
- *The fatal SAE of left ventricular dysfunction was reported for a 76-year-old male patient who was hospitalized due to left ventricular diastolic dysfunction secondary to known coronary ischemia and hypertension. Seven days following event onset he passed away at home.*

No deaths were reported in any of the supportive literature that was reviewed or among the 960 patients that receiving one dose of the FDA-approved Gallium Ga 68 PSMA-11 Injection.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. It is highly possible that the death of the 3 patients are not related to GOZ administration.

Serious Adverse Events

The Applicant’s Position:

Overall, SAEs were reported for 16 patients (1.6%) (Table 15) and none were suspected to be causally related to administration of GOZ. One SAE of hyponatremia was reported to be related to study drug; this was considered related to enzalutamide and unrelated to GOZ.

Table 15. GOZ Serious Treatment Emergent Adverse Events Regardless of GOZ Relationship by PT (Study PSMA-617-01, PSMA-11 Safety Analysis Set)

Preferred Term	Overall (N=1003)	
	All Grades n (%)	Grade ≥3 n (%)
Number of patients with at least one event	16 (1.6)	15 (1.5)
Spinal cord compression	2 (0.2)	2 (0.2)
Acute kidney injury	1 (0.1)	1 (0.1)
Ascites	1 (0.1)	1 (0.1)
Bicytopenia	1 (0.1)	1 (0.1)
Cardio-respiratory arrest	1 (0.1)	1 (0.1)
Gastritis	1 (0.1)	1 (0.1)
Hyponatremia	1 (0.1)	1 (0.1)
Intracranial pressure increased	1 (0.1)	1 (0.1)
Large intestinal obstruction	1 (0.1)	1 (0.1)
Left ventricular dysfunction	1 (0.1)	1 (0.1)
Pain	1 (0.1)	1 (0.1)
Pulmonary embolism	1 (0.1)	1 (0.1)
Subdural hematoma	1 (0.1)	1 (0.1)
Tumor associated fever	1 (0.1)	0
Urinary tract infection pseudomonal	1 (0.1)	1 (0.1)

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

GOZ Treatment-emergent adverse event (TEAE) = any AE within 6 days of GOZ dosing or any treatment related AE > 6 days from GOZ dosing as long as prior to first dose of randomized treatment. Relatedness was not distinguished between GOZ and BSC/BSoC.

Numbers (n) represent counts of patients.

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

MedDRA version 23.1, NCI CTCAE version 5.0.

Abbreviations: GOZ, Ga68-gozetotide; PSMA, prostate-specific membrane antigen

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No SAEs were reported in any of the supportive safety publications.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

As GOZ PET/CT scan was done only once, and, therefore, it was not appropriate to collect information on AEs leading to discontinuation or dose interruption/adjustment. However, 2 patients were not enrolled to the randomized treatments due to AEs.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Significant Adverse Events

The Applicant's Position:

In Study PSMA-617-01, GOZ TEAEs $\geq$ Grade 3 were reported in 2.1% of subjects, see Table 16.

The FDA's Assessment:

Based on the Table 16, GOZ TEAEs $\geq$ Grade 3 were reported in 15 subjects, which is 1.5 % instead of 2.1%. This typo will not affect the evaluation of the safety of GOZ.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Overall, 12.2% of patients reported at least one AE, and 5.5% had at least one AE considered by the investigator to be related to study drug (related to GOZ and/or BSC/BSoC, AE relatedness was not distinguished between BSC/BSoC or GOZ). Very few patients had SAEs (1.6%) or high-grade AEs (grade $\geq$ 3, 2.1%). Three patients had a fatal event; none was related to GOZ (Table 16).

Table 16. Overview of GOZ AEs (PSMA-11 Safety Analysis Set)

AE Category	Overall N=1003 n (%)
AE	122 (12.2)
Serious AE	16 (1.6)
Grade 3/4/5 AE	21 (2.1)
Drug-related AE	55 (5.5)
Serious drug-related AE	1 (0.1)
Drug-related grade 3/4/5 AE	4 (0.4)
Fatal AE	3 (0.3)

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

"Drug-related" as per Investigator assessment. AE relatedness was not distinguished between BSC/BSoC or GOZ.

Abbreviations: AEs, adverse events; Ga68-gozetotide; N, number of subjects; n, number of subjects within specific category; PSMA, prostate-specific membrane antigen

TEAEs were reported most frequently in the system organ classes (SOCs) of gastrointestinal disorders, general disorders and administrative site conditions, and musculoskeletal and connective tissue disorders. Fatigue was reported in 1.2% of patients; all other events were reported in less than 1.0% of patients (Table 17).

Table 17. GOZ TEAEs Occurring in at Least 0.5% of Patients Regardless of GOZ Relationship by Preferred Term and Maximum Grade (PSMA-11 Safety Analysis Set)

Preferred Term	Overall N=1003	
	All Grades n (%)	Grade ≥ 3 n (%)
Patients with at least one event	122 (12.2)	21 (2.1)
Fatigue	12 (1.2)	1 (0.1)
Asthenia	9 (0.9)	0
Back pain	8 (0.8)	0
Nausea	8 (0.8)	0
Anemia	7 (0.7)	0
Lymphopenia	6 (0.6)	2 (0.2)
Oedema peripheral	6 (0.6)	0
Constipation	5 (0.5)	0
Decreased appetite	5 (0.5)	0
Vomiting	5 (0.5)	0

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

Numbers (n) represent counts of patients.

A patients with multiple severity grades for a PT is only counted under the maximum grade.

MedDRA version 23.1, CTCAE version 5.0.

Abbreviations: GOZ, Ga68-gozetotide; PSMA, prostate-specific membrane antigen; TEAEs, treatment-emergent adverse events

To enable a closer comparison of AE data from Study PSMA-617-01 with the supportive data sources (Section 8.2.1), an analysis of TEAEs was performed limiting the time window to the day of or the day after ⁶⁸Ga-PSMA-11 injection. Within this shorter time window 20 patients (2.0%) had TEAEs, regardless of drug-relationship, and all events were reported in less than 0.5% of patients, all were of Grade 1-2 severity except for 1 Grade 3 (fatigue) and 1 Grade 5 (Subdural hematoma) event.

Common AEs by SOC and PT in the supportive Safety Publications

No AEs were reported in any of the supportive safety publications with the exception of the prospective study by (Fendler et al. 2019), where no grade 2 or higher events were reported. Overall, 15 of 635 patients (2%) experienced grade 1 events. The most frequently reported events were diarrhea (3 patients), nausea (2 patients) and headache (2 patients). The authors made no specific causality assessments.

Common AEs for ⁶⁸Ga-PSMA-11 Approved by FDA

In the recent FDA approved Gallium Ga 68 PSMA-11, the most common AEs reported were diarrhea, dizziness, and nausea/vomiting. All AEs were classified as grade 1 (FDA 2020a, FDA 2020b).

The FDA's Assessment:

FDA agrees with the Applicant's evaluation of Treatment Emergent Adverse Events and Adverse Reactions of GOZ. The drug related TEAE in the safety population in VISION are

listed in Table 18, and the TEAEs in the safety population of Studies PSMA-PreRP and PSMA-BSR of RLD are listed in Table 19.

Table 18. Drug Related Treatment-Emergent Adverse Events in the Safety Population in VISION
VISION Safety Set (N=1003)

MedDRA SOC or PT	n (%)
Blood and lymphatic system disorders	13 (1.3)
Anemia	5 (0.5)
Lymphopenia	5 (0.5)
Leukopenia	1 (0.1)
Neutropenia	1 (0.1)
Normocytic anemia	1 (0.1)
Ear and labyrinth disorders	1 (0.1)
Ear pruritus	1 (0.1)
Gastrointestinal disorders	18 (1.8)
Nausea*	6 (0.6)
Dry mouth*	3 (0.3)
Abdominal pain	2 (0.2)
Constipation*	2 (0.2)
Diarrhea*	2 (0.2)
Dyspepsia	1 (0.1)
Abdominal pain upper	1 (0.1)
Stomatitis	1 (0.1)
General disorders and administration site conditions	23 (2.3)
Fatigue*	10 (1.0)
Asthenia	6 (0.6)
Oedema peripheral	2 (0.2)
Influenza like illness	1 (0.1)
Injection site hematoma*	1 (0.1)
Injection site warmth*	1 (0.1)
Malaise	1 (0.1)
Chills*	1 (0.1)
Investigations	5 (0.5)
Weight decreased	2 (0.2)
Alanine aminotransferase increased	2 (0.2)
Aspartate aminotransferase increased	1 (0.1)
Metabolism and nutrition disorders	4 (0.4)
Decreased appetite	3 (0.3)
Hyponatremia	1 (0.1)
Musculoskeletal and connective tissue disorders	6 (0.6)
Back pain	2 (0.2)
Bone pain	2 (0.2)
Flank pain	1 (0.1)
Myalgia	1 (0.1)
Nervous system disorders	3 (0.3)
Cognitive disorder	1 (0.1)
Dizziness	1 (0.1)
Peripheral sensory neuropathy	1 (0.1)

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Respiratory, thoracic, and mediastinal disorders	1 (0.1)
Productive cough	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.2)
Dry skin	1 (0.1)
Rash	1 (0.1)
Vascular disorders	2 (0.2)
Deep vein thrombosis	1 (0.1)
Hypertension	1 (0.1)
Patients with any adverse event	55 (5.5%)

Source: FDA clinical reviewer analysis.

* indicates that the adverse event was considered related to GOZ only.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, number of subjects within specific category; PT, preferred term; SOC, system organ class

Table 19. Treatment-Emergent Adverse Events in the Safety Population of Studies PSMA-PreRP and PSMA-BCR

MedDRA SOC or PT	Pooled Safety Set (N=960) N (%)	UCSF Safety Set (N=597) N (%)
Gastrointestinal disorders	11 (1.1%)	8 (1.3%)
Diarrhea**	4 (0.4%)	4 (0.7%)
Nausea**	4 (0.4%)	2 (0.3%)
Vomiting**	1 (0.1%)	1 (0.2%)
Dysphagia	1 (0.1%)	1 (0.2%)
Abdominal discomfort	1 (0.1%)	0
Nervous system disorders	8 (0.8%)	8 (1.3%)
Dizziness	4 (0.4%)	4 (0.7%)
Headache	2 (0.2%)	2 (0.3%)
Lethargy	1 (0.1%)	1 (0.2%)
Hypoesthesia**	1 (0.1%)	1 (0.2%)
General disorders and administration site conditions	5 (0.5%)	5 (0.8%)
Fatigue**	2 (0.2%)	2 (0.3%)
Injection site pruritus	1 (0.1%)	1 (0.2%)
Pain**	1 (0.1%)	1 (0.2%)
Asthenia	1 (0.1%)	1 (0.2%)
Renal and urinary disorders	4 (0.4%)	4 (0.7%)
Bladder pain	1 (0.1%)	1 (0.2%)
Bladder spasm	1 (0.1%)	1 (0.2%)
Urinary retention	1 (0.1%)	1 (0.2%)
Nephrolithiasis	1 (0.1%)	1 (0.2%)
Psychiatric disorders	2 (0.2%)	2 (0.3%)
Initial insomnia	1 (0.1%)	1 (0.2%)
Autoscopy	1 (0.1%)	1 (0.2%)
Vascular disorders	2 (0.2%)	2 (0.3%)
Hypotension	1 (0.1%)	1 (0.2%)
Hot flush**	1 (0.1%)	1 (0.2%)
Eye disorders	1 (0.1%)	1 (0.2%)
Vision blurred	1 (0.1%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.1%)	1 (0.2%)
Muscular weakness**	1 (0.1%)	1 (0.2%)
Skin and subcutaneous tissue disorders	1 (0.1%)	1 (0.2%)
Rash	1 (0.1%)	1 (0.2%)
Patients with any adverse event	28 (2.9%)	25 (4.2%)

Source: FDA clinical reviewer analysis.

** indicates that the adverse event was considered possibly, probably, or definitely related to study drug administration in at least 1 patient

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients, PT = preferred term, SOC = system organ class, UCSF = University of California, San Francisco

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212642Orig1s000MutlidisciplineR.pdf

Adverse Drug Reactions

The Applicant's Position:

Screening for candidates for ADRs was performed by applying both quantitative and qualitative criteria to AE data from Study PSMA-617-01. ADRs were determined from Study PSMA-617-01 by applying plausibility criteria and medical judgment to all TEAEs with incidence $\geq 0.3\%$, all TEAEs occurring on the day of GOZ administration or the day thereafter, serious TEAEs not considered to be disease progression, all event terms defined as designated medical events, and considering data from other literature sources.

The results of this ADR selection are provided Table 20. Mild to moderate adverse drug reactions (ADRs) occurred in patients receiving GOZ, with the exception of a Grade 3 fatigue event (0.1%). No serious adverse drug reactions occurred in patients receiving GOZ. The most common adverse drug reactions of any grade (incidence $\geq 0.5\%$) are fatigue (1.2%), nausea (0.8%), constipation (0.5%) and vomiting (0.5%).

Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 20. Adverse Drug Reactions Observed With Gallium (68Ga) Gozetotide in the VISION Clinical Study

Adverse Drug Reactions	Gallium (68Ga) gozetotide 0.9-3.7 MBq/kg N=1003 n (%)	Frequency Category N=1003
	All Grades	All Grades
Gastrointestinal disorders		
Nausea	8 (0.8)	Uncommon
Constipation	5 (0.5)	Uncommon
Vomiting	5 (0.5)	Uncommon
Diarrhea	4 (0.4)	Uncommon
Dry mouth	4 (0.4)	Uncommon
General disorders and administration site conditions		
Fatigue	12 (1.2)	Common
Injection site reactions ¹	2 (0.2)	Uncommon
Chills	1 (0.1)	Uncommon

Source: NDA215841\0000\m1\us\ fda-response-multidisciplinary-assessment-aid.docx

¹ Injection site reactions includes: Injection site hematoma, injection site warmth

Abbreviations: N, number of subjects; n, number of subjects within specific category

FDA Assessment:

In general, FDA agrees the Applicant's assessment of ADRs. Within Study PSMA-617-01 the treatment-emergent period was defined as the period from the date of GOZ dosing up to 6 days after the date of GOZ dosing as long as this was prior to Cycle 1 Day 1 (C1D1). Therefore, it might be challenging to separate the AEs induced by GOZ and AEs resulted from BSoc, especially in a patient population with relatively late stage of the disease.

Laboratory Findings

The Applicant's Position:

Laboratory parameters were not specifically assessed post-dosing for GOZ in Study PSMA-617-01.

No safety concerns related to laboratory abnormalities were reported in the supportive safety publications.

The FDA's Assessment:

In the approved 68Ga-PSMA-11 NDAs (NDAs 212642/212643), clinical laboratory testing was not performed. In view of the microdose of GOZ (less than 25 µg and 3-7 mCi) and the anticipated infrequent administration, it is reasonable to assume that the likelihood of a meaningful effect on laboratory values is low. The review team agrees with the Applicant that no safety concerns related to laboratory abnormalities were reported in the literature. In addition, the FDA guidance for industry Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments states that for lower risk (Group 1) agents like GOZ, a less extensive clinical safety evaluation is appropriate. Therefore, the absence of clinical laboratory testing was considered acceptable.

Vital Signs

The Applicant's Position:

Vital signs were not specifically assessed post-dosing for GOZ in Study PSMA-617-01.

In the publication by (Nielsen et al. 2017), blood pressure was assessed at baseline, upon injection of GOZ, at 1, 10 and 60 minutes post-injection, as well as post-scan in 88 patients. During this observation period, systolic BP increased by 1 CTCAE grade in 15 patients and by 2 grades in 2 patients, with most cases of hypertension resolving spontaneously.

The FDA's Assessment:

In approved NDAs 212642/212643, assessment of vital sign data was by shift table, by correlation of changes in vital signs to GOZ dose, and by examination of patients with the largest changes. No findings were identified to suggest a meaningful effect of GOZ on heart rate or blood pressure. Therefore, the absence of vital signs in VISION study was considered acceptable.

Electrocardiograms (ECGs)

The Applicant's Position:

ECGs were not specifically assessed post-dosing for GOZ in Study PSMA-617-01.

The FDA's Assessment:

Electrocardiograms (ECGs) were not obtained in either of the trials that enrolled the safety population. One published report states that there was no change in ECG after administration of 3.2 to 4.3 mCi GOZ in five patients with known or suspected prostate cancer (Pfob et al. 2016).

QT

The Applicant's Position:

There is no known mechanism that would suggest a risk of QT prolongation associated with the administration of GOZ. The potential risk of QT/QTc interval prolongation would be considered low due to the sub-pharmacologic nature of the agent, the very low administered dose, and the lack of distribution and retention in cardiac muscle. GOZ has a short biological half-life and physical half-life, and when combined with the low administered dose, the systemic exposure is

very low. PSMA is not expressed on cardiomyocytes, and the exposure level to the heart, as measured by dosimetry, is not notable.

Regarding clinical studies of PSMA-11 and literature, no AEs regarding an increase in QT prolongation have been observed and no evidence of QT prolongation or arrhythmias following administration of GOZ. Given these points, it is considered that the risk of QT prolongation appears to be low.

In the safety study by (Nielsen et al. 2017), HR was assessed at baseline and immediately following administration of GOZ, as well as at 1, 10 and 60 minutes post-injection, and following image acquisition. Mean HR decreased from 67 to 62 bpm, resulting in a number of patients with grade 1 (asymptomatic) bradycardia, primarily in patients with preexisting bradycardia. No events of grade 2 bradycardia or higher were observed. Transient grade 1 tachycardia developed in 1 patient. None of the changes in HR required medical intervention.

The FDA's Assessment:

No formal QT study was performed for this single administration microdose drug and no study was needed.

Immunogenicity

The Applicant's Position:

Not applicable

The FDA's Assessment:

The review team agrees that immunogenicity evaluation was not needed for this single administration microdose drug.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

There are no specific safety issues to discuss.

The FDA's Assessment:

The review team agrees with the Applicant's position.

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

The Applicant's Position:

COA data were not collected.

The FDA's Assessment:

The FDA acknowledges the Applicant's position.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

AEs for GOZ were analyzed for the PSMA-11 Safety Analysis Set by subgroups based on age, renal function, liver function, region, dose administered, concomitant therapies (concurrent use of BSC/BSoC and NAADs), radiotherapy, and imaging procedures. The data do not suggest that any of the subgroups influenced the likelihood or severity of AE.

In the supportive literature sources, no subgroup analyses were reported. For the recently FDA-approved GOZ Injection, no special concern was noted for analyses of AEs by age (FDA 2020a; FDA 2020b).

The FDA's Assessment:

The review team agrees with the Applicant's position. In addition, the relatively small number of AE reports prevent meaningful subgroup analyses for age, race, or ethnicity.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

The safety of GOZ in special populations was not assessed in dedicated studies. No studies in special patient populations have been reported in the selected literature.

The FDA's Assessment:

The review team agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No studies of carcinogenicity were performed and none are needed. As with all radioactive drugs, there is believed to be a low, dose-dependent risk for induction malignancy.

The FDA's Assessment:

The review team agrees with the Applicant's position for this one time administered microdose drug.

Human Reproduction and Pregnancy

The Applicant's Position:

The safety and efficacy of GOZ has not been established in females, as GOZ is not indicated for use in females.

The FDA's Assessment:

The FDA agrees with the Applicant's Position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

The safety and efficacy of GOZ has not been established in pediatrics, as GOZ is not indicated for use in pediatric patients.

The FDA's Assessment:

The review team agrees with the Applicant's Position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose

In Study PSMA-617-01, the profile of AEs reported for patients who received actual GOZ doses ≥ 5 mCi was similar/comparable to that of the patients who received actual GOZ less than 5 mCi. In Study PSMA-617-01, the actual dose administered to patients ranged from 92.8 MBq (2.5 mCi) to 287.5MBq (7.8 mCi), with a corresponding body weight adjusted dose range of 0.9-3.7 MBq per kg (median dose: 1.9 MBq/kg) and this dose range was associated with a favorable safety profile.

There is no experience with overdose of GOZ. An overdose in the pharmacological sense is unlikely given the microdose used for imaging for patient selection purposes and the fact that the product is not self-administered by the patient.

Doses of up to 400 MBq have been reported in the literature, without any adverse safety effects (Afshar-Oromieh et al. 2017). In the event of administration of a radiation overdose with GOZ, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by hydration and frequent bladder voiding.

Drug Abuse

There is no experience with drug abuse of GOZ. There is no known dependence potential for GOZ.

Withdrawal and Rebound

No studies have specifically examined the withdrawal or rebound effects of GOZ but no such effects are expected from this radioimaging agent intended for single use.

The FDA's Assessment:

The review team agrees with the Applicant's Position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Another GOZ product was approved in Dec-2020 by the FDA. Two marketing authorizations have been granted, one to UCLA and one to UCSF and no post-marketing data have been publicly reported as of the Study PMSA-617-01 cut-off date (27-Jan-2021).

A worldwide literature search for clinical safety data relevant to GOZ was conducted in the context of routine pharmacovigilance. Medline, Embase and Biosis databases were searched using terms related to the 68-Gallium label in combination with the peptide targeted based action with related synonyms and standard safety filters. Ongoing pharmacovigilance of systematic searches of the literature for signal detection covering >10 years of GOZ investigative/compassionate use and/or expanded access, up to a date of 20-Feb-2021, revealed no additional safety signals.

The FDA's Assessment:

The review team agrees with the Applicant's Position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the approved labels for the already approved GOZ product and the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse reactions.

The FDA's Assessment:

The review team agrees with the Applicant's Position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The Phase III clinical Study PSMA-617-01 provides safety data for single-administration of ⁶⁸Ga-PSMA-11 in 1003 patients with mCRPC, the largest safety dataset from a prospective study to date for characterizing the safety profile of GOZ in patients with prostate cancer. Overall, 12.2% of patients had AEs in the defined treatment-emergent period in the days following GOZ administration, which could also have been related to best supportive care or best standard of care agents. The most frequent AE was fatigue (1.2%) and all other events were reported in less than 1.0% of patients. Overall, 5.5% of AEs were considered drug-related by the investigator (AE relatedness was not distinguished between BSC/BSoc or GOZ). Within a 2-day observation window, AEs were reported in 2.0% of patients and drug-related AEs in 0.5% of patients.

Three patients (0.3%) had a SAE leading to fatal outcome, which were likely attributable to the patients' underlying advanced disease. SAEs were reported in 1.6% of patients; none of the SAEs were causally related to GOZ. AEs of $\geq$ Grade 3 in severity were reported in 2.1% of patients; these events were consistent with expected effects due to the mode of action of

BSC/BSoC concomitant treatments, or reflective of the pretreatment/disease background of these mCRPC patients. As best as the safety profile of GOZ could be discerned against this background, few ADRs could be identified.

No major safety issues have been reported in supportive literature following extensive use of GOZ (> 3000 patients). Although the patients in Study PSMA-617-01 had more advanced disease than the patients in the supportive safety sources and were heavily pre-treated, there was consistency in the most frequently reported AEs for GOZ. The higher incidence of AEs in Study PSMA-617-01 compared to the supportive literature and the recently FDA-approved ⁶⁸Ga-PSMA-11 is expected given the conservative AE observation window and the patient population with more advanced disease in Study PSMA-617-01.

In Study PSMA-617-01 the actual dose administered to patients ranged from 92.8 MBq (2.5 mCi) to 287.5 MBq (7.8 mCi), with a corresponding body weight adjusted dose range of 0.9-3.7 MBq per kg (median dose: 1.9 MBq/kg). This dose range was associated with a favorable safety profile and is in line with the effective dose of GOZ across the safety publications, which ranged from 0.0158 to 0.0258 mSv/MBq.

Overall, GOZ was well tolerated in Study PSMA-617-01. As with other radioactive diagnostic agents with microdose active substances and single administration, and as expected from the nonclinical data and pharmacological properties, only a small number of events, mostly Grade 1-2, were reported and no new safety signals were identified.

The key risks in the use of GOZ are the risks of misdiagnosis and radiation exposure. Misdiagnosis is an inherent risk for any diagnostic procedure. GOZ uptake on PET images is not specific to prostate cancer and occurs in some normal organs as per its biodistribution, and in other types of cancer as well as nonmalignant lesions. The risk of misdiagnosis, whether as a false negative or a false positive, can have clinically significant impact on patient management. Given the consistent interpretation of the scans and the good sensitivity and specificity for GOZ PET/CT, the magnitude of the risk is considered lower than currently available imaging modalities in this setting, e.g. CT, MRI, bone scan, and, as a minimization strategy, the labeling intends to recommend that the interpretation of PET imaging findings should be made in the context of the patient history and other diagnostic procedures. For primary staging, the false positive and false negative in (Hofman et al. 2020) were 2/145 (1.4%) and 6/145 (4.1%), respectively. For restaging, the false positive and false negative in (Fendler et al. 2019) were 14/87 (16.1%) and 8/87 (9.2%), respectively. The risk of radiation exposure from GOZ is its contribution to the patient's overall long-term cumulative radiation exposure, which in turn may represent an increased risk of cancer. For a 7 mCi (259 MBq) dose of GOZ, the absorbed dose would be 6.68 mSv, which is in range with other standard-of-care radio-diagnostic procedures (e.g. a diagnostic CT scan would lead to approximately 13-15 mSv).

None of the safety observations negatively impact the benefit-risk balance of GOZ at this dose across patient populations in prostate cancer.

The FDA's Assessment:

FDA generally agrees with the Applicant's safety assessment that GOZ was well tolerated in VISION. Review issues related to risk of misdiagnosis may also have safety implications; for this diagnostic imaging product, these issues are covered under Section 8.1 (efficacy review).

9 Summary And Conclusions

9.1. Statistical Issues

This section pertains to the statistical review of reviewer variability study (kappa study) and the quantitative analysis requested by the FDA review team. This kappa study was performed as part of the data evidence on inter-reader and intra-reader agreement to support the proposed patient selection indication of the investigational imaging agent GOZ for PET in prostate cancer patients. In the VISION trial, the main therapeutic phase 3 clinical trial, GOZ PET was used to select prostate cancer patients who met VISION PET inclusion criteria based on their GOZ PET scans. That is, only patients with at least one PSMA scan-positive lesion identified on PSMA-PET/CT and no PSMA scan-negative lesion fulfilling the exclusion criteria were to be enrolled in the study, provided all other inclusion criteria were met. Eligible prostate cancer patients were randomized to receive either VIP plus standard of care or standard of care alone to evaluate the therapeutic efficacy of VIP.

9.1.1. VISION Reviewer Variability Study

There were three independent readers participating in the reviewer variability study. The three readers were experienced, U.S. board certified nuclear medicine physicians with two of the readers being dual board certified in radiology. To provide training for the readers on the VISION PET/CT scan read criteria prior to the independent blinded read, an Independent Review Training Manual was developed. A nuclear medicine radiologist involved in the development of the VISION read criteria was assigned as the trainer. Initially, an in-person training session was planned. However, due to the COVID-19 pandemic, an interactive remote training program developed by the trainer was conducted virtually. During training, the trainer guided the readers through the training manual, software review, and training cases. The Applicant indicated that the scoring of the training cases was performed in a manner similar to the actual blinded read. The readers were trained to evaluate the cases systematically and to become familiar with the image review software and eCRF.

The following topics were covered during the reader training session:

- Overview of Independent Review sessions and environment
- Overview of GOZ imaging and assessment of eligibility criteria
- Suggested search pattern
- Review of testing cases
- Independent assessment of 10 testing cases

After completing the training session, the readers were proficiency tested with 10 testing cases. Readers were required to correctly assess at least 80% of the cases before proceeding to the independent review session. All readers scored 80% or higher on the 10 initial testing cases.

In the reviewer variability study, 125 PET scans consisting of 75 scans from patients included in the VISION trial (inclusion cases) and 50 scans from patients excluded from the VISION trial (exclusion cases) were randomly chosen. Three independent PET readers interpreted the 125 PET scans according to Vision PET read criteria for inclusion or exclusion for treatment. Inter-reader agreement was assessed by testing if Fleiss kappa was greater than 0.52. Twenty of the

125 PET scans (12 scans from inclusion cases and 8 scans from exclusion cases) were recoded for repeat reads for the evaluation of intra-reader agreement using Cohen’s kappa. Note that Cohen’s kappa is the same as Fleiss kappa for a 2x2 agreement analysis. For the rest of Section 9.1, the term Fleiss kappa will be used.

Figure 8. Inter-Reader Agreement Evaluation

$$\begin{aligned}
 &Var(\text{Fleiss kappa}) \\
 &= \frac{2}{Nn(n-1)} \times \frac{(\sum_j p_j(1-p_j))^2 - \sum_j p_j(1-p_j)(1-2p_j)}{(\sum_j p_j(1-p_j))^2}
 \end{aligned}$$

Source: (Fleiss 1971)

As a rule of thumb, a Fleiss Kappa estimated to be 0.60, indicates moderate inter-reader agreement.¹ The point estimate and the 95% confidence interval for Fleiss kappa in the reviewer variability study is 0.60 (0.50 - 0.70) using the standard error from the following formula (Fleiss et al. 2003).

where *N* represents the total number of subjects (125 subjects in this study), *n*, the number of ratings per subject (3 ratings per subject in this study) and *p_j*, the proportion of ratings assigned to the *j*th category out of all *N* × *n* ratings (*j* = yes or no in this study).

Since the lower bound of the 95% confidence interval does not meet the pre-specified threshold of 0.52, the reviewer variability study is not deemed successful. Not meeting the 0.52 threshold does not necessarily indicate there is no agreement among PET readers. As Fleiss kappa of 0 implies that the agreement among readers is by chance, the lower bound of 0.50 indicates some agreement beyond chance.

The statistical reviewer performed the following investigation. When investigating reader agreement in inclusion cases and exclusion cases separately, strong agreement was observed for 75 PET scans from patients eligible for treatment in the VISION trial as shown in Table 21. Three readers agreed for 88% of the 50 inclusion cases by reading as inclusion. For a patient to be eligible for treatment in the VISION trial, the patient should have at least 1 PET-positive lesion without any PET-negative lesion meeting the pre-specified selection criteria.

Table 21. Reader Agreement in 75 Inclusion Cases

Inclusion Cases	Frequency	Percentage (%)
Read as inclusion by all 3 readers	66	88
Read as inclusion by 2 readers and as exclusion by 1 reader	7	9
Read as inclusion by 1 reader and as exclusion by 2 readers	2	3
Read as exclusion by all 3 readers	0	0
Total	75	100

Source: FDA statistical reviewer analysis

On the other hand, weak agreement was observed for 50 PET scans from patients ineligible for treatment in the VISION trial as shown in Table 22. Twenty percent (10 of the 50 exclusion cases) were read in an opposite direction, i.e., should have been included in the VISION trial, by all 3 readers. Per the study protocol, any PET-negative lesion meeting exclusion criteria, regardless of existence of PET-positive lesion, excluded a patient from treatment eligibility in the VISION trial.

Table 22. Reader Agreement in 50 Exclusion Cases

Exclusion Cases	Frequency	Percentage (%)
Read as exclusion by all 3 readers	20	40
Read as exclusion by 2 readers and as inclusion by 1 reader	7	14
Read as exclusion by 1 reader and as inclusion by 2 readers	13	26
Read as inclusion by all 3 readers	10	20
Total	50	100

Source: FDA statistical reviewer analysis

Intra-Reader Agreement Evaluation

The intra-reader agreement for each reader is acceptable. Readers 1, 2 and 3 all interpreted most of the 20 PET scans recoded for repeat reads the same at the first and the second reads as shown in Table 23, Table 24, and Table 25 (i.e., read as inclusion at both the first and the second reads and as exclusion at both the first and the second reads).

Table 23. Intra-Reader Agreement for Reader 1

Reader 1 Cohen's Kappa = 0.78 (95% Confidence Interval: 0.49 – 0.99)		Second Read	
		Inclusion	Exclusion
First read	Inclusion	12	1
	Exclusion	1	6

Source: FDA statistical reviewer analysis

Table 24. Intra-Reader Agreement for Reader 2

Reader 2 Cohen's Kappa = 0.76 (95% Confidence Interval: 0.46 – 0.99)		Second Read	
		Inclusion	Exclusion
First read	Inclusion	13	0
	Exclusion	2	5

Source: FDA statistical reviewer analysis

Table 25. Intra-Reader Agreement for Reader 3

Reader 3 Cohen's kappa = 0.89 (95% confidence interval: 0.67 – 0.99)		Second Read	
		Inclusion	Exclusion
First read	Inclusion	13	1
	Exclusion	0	6

Source: FDA statistical reviewer analysis

Additional Exploratory Evaluation

The reviewer variability study read results from the three independent readers were compared to the VISION eligibility read results used to determine patient enrollment into the study. Table 26 was created from Table 21 and Table 22 by the counts of actual inclusion and exclusion cases in the VISION trial out of the cases assessed as inclusion or exclusion by majority read, i.e., assuming at least 2 out of 3 readers must agree with the image read decision, in the reviewer variability study.

Table 26. Inter-Reader Agreement for Reviewer Variability Consensus Read

Reviewer Variability Study	VISION Study Central Reader	
	Inclusion*	Exclusion
Consensus of 3 Readers		
Inclusion	73	23
Exclusion	2	27
Total number of patients	75	50

Source: FDA Tables 1 and 2 in Section 8.3 and assumes that at least 2 out of 3 readers agree with the image read decision in the reader variability study mimics blinded independent central read criteria in the VISION trial

In this exploratory analysis, the Fleiss kappa is estimated as 0.55 with 95% CI (0.4, 0.7). Multiple authors have proposed how kappa measure can be interpreted. Below is one such example from (Landis and Koch 1977).

Kappa Interpretation

- < 0 Poor agreement
- 0.01 - 0.20 Slight agreement
- 0.21 - 0.40 Fair agreement
- 0.41 – 0.60 Moderate agreement
- 0.61 - 0.80 Substantial agreement
- 0.81 - 1.00 Almost perfect agreement

Research (Dunn 1989) indicates that the following factors influence kappa value: reader accuracy, number of ratings in the set, prevalence of specific ratings, reader bias, and reader independence. In binary (positive, negative) classification, kappa value needs to be interpreted with caution because, as per statistical and clinical literature, prevalence variability has the strongest impact on kappa value and can lead to the same kappa value for various reader accuracy vs. prevalence variability combinations.

In the VISION trial, the following table (Table 27) was derived from responder status for PFS and PSA parameters (as a secondary endpoint) based on the PSMA positive scan patients selection via pre-specified inclusion criteria mentioned earlier. This secondary endpoint (responder status) was chosen given its inclusion of PFS and PSA parameters and the observed small effect estimate among all primary and secondary endpoints.

Table 27. Responder Analysis in the VISION Trial Using One Central Eligibility Read

VISION Study	Experimental Treatment	Standard Treatment
Responder	177	14
Non-responder	208	182
Total	385	196

Source: extracted from the sponsor report of study PSMA-617-01 synopsis page 6.

Hypothetically, if the sponsor took reviewer variability consensus read as the primary method for inclusion in the VISION trial, then 23 additional patients would have been included, and 2 currently included patients would have been excluded. Included patients would get randomized in 2:1 ratio to experimental treatment (~15 patients) and standard treatment (~8 patients). The most conservative analysis of these patients would be where 2 excluded patients were in experimental treatment arm and were responders, 15 additional patients in experimental treatment arm were all non-responders and 8 additional patients in standard treatment arm were all responders. This hypothetical scheme would have given a conservative treatment effect estimate on response rate difference, see Table 28.

Table 28. Responder Analysis for VISION Trial Using Reviewer Variability Consensus Eligibility Read

VISION Study	Experimental Treatment	Standard Treatment
Responder, n (%)	175 (44%)	22 (11%)
Non-responder	223	182
Total	398	204

Source: FDA statistical reviewer analysis

The estimated response rate difference (experimental treatment – standard treatment) would have been 33% with 95% CI (25.5%, 40.5%), a secondary efficacy endpoint. In this hypothetical scenario, it appears that the experimental treatment (VIP) suggests efficacy on response rate for the patient population with progressive PSMA-positive mCRPC using central consensus read. This exploratory analysis seems to suggest that patients with GOZ scans selected on the basis of input from multiple readers might benefit from VIP.

Summary of Statistical Evaluations on Reader Variability Study

Inter-reader agreement (Fleiss kappa) did not meet the pre-specified threshold in the reviewer variability study. However, the lower bound of 0.50 indicates that there is some agreement beyond chance among readers. The lower bound of the 95% confidence interval of Fleiss kappa being lower than the pre-specified threshold of 0.52 is affected by weak agreement in PET scans from 50 patients excluded from the VISION trial.

It is worthwhile to note that to maximize treatment benefits of VIP, the exclusion criteria emphasized the identification of discordance between measurable lesions on CT/MRI and negative lesions on GOZ PET/CT, regardless of the presence of other PSMA-positive lesions. Identification of negative lesions is inherently more challenging as it requires the readers to search for anatomical lesions on CT/MRI with no or low corresponding image tracer uptake on PET. As mentioned in the Applicant's study report, in the VISION trial, only ~5% of exclusion cases were attributed to a fully negative GOZ scan, whereas most patients showed PSMA-positive scans but were excluded based on the presence of at least one PSMA-negative lesion. These criteria likely lead to the observation of higher agreement rate between inclusion cases compared to exclusion cases in this study.

The above statistical summary focused on the PSMA scan results and did not consider whether all other inclusion criteria were met for the VISION trial.

9.1.2. Quantitative Analysis in mCRPC Patients Receiving VIP+ BSC/BSoC

This quantitative analysis was conducted by the applicant as a sub-study of the pivotal VISION study upon FDA review-team's request.

The primary objective of the quantitative analysis was to examine the association between rPFS and tumor burden/characteristics derived from GOZ PET scans obtained at the time of enrollment into the VISION study. The secondary objective was to examine the association between OS/objective response rate (ORR)/prostate-specific antigen (PSA) response and tumor burden/characteristics.

To participate in the quantitative analysis study, subjects had to be enrolled into the investigational arm (VIP plus BSC/BSoC). The total available number of subjects for inclusion

in the quantitative analysis study was 548 as 551 subjects were randomized to the investigational arm of the VISION study, but 3 subjects did not have images that met the quality requirements.

Quantitative imaging data including overall tumor burden and radiotracer uptake within anatomical regions of bone, liver, lymph nodes and soft tissues and imaging-based tumor characteristics were extracted from baseline GOZ PET scans by a sponsor-designated company ((b) (4) Imaging data for the whole body was represented by the combination of all segmented regions.

For the whole-body region, the analysis included the following variables:

- Presence of PSMA+ lesion in the liver (Yes/No)
- Presence of PSMA+ lesion in the bones (Yes/No)
- Presence of PSMA+ lesion in the lymph nodes (Yes/No)
- Presence of PSMA+ lesion in the soft tissue (Yes/No)
- Whole body SUV_{mean}
- Whole body SUV_{max}
- Whole body tumor volume
- Whole body tumor load

For each of the anatomical regions, the analysis included the following variables for each region and only included patients with at least a PSMA+ lesion in that specific anatomical region:

- SUV_{mean}
- SUV_{max}
- Tumor volume
- Tumor load

To identify covariates associated with rPFS in each anatomical region as well as whole body region, a Cox proportional hazards model was fitted in the following order:

- (1) Univariate Cox proportional hazards model was used to assess the individual predictive value of each baseline GOZ PET scan covariate on rPFS: imaging covariates found to be individually related to rPFS (2-sided p-value < 0.05) were included in a multivariate Cox model.
- (2) Backwards elimination procedure was utilized to the multivariate Cox model: remove a covariate with the highest 2-sided p-value (as soon as ≥ 0.05), re-run the model without the covariate identified and repeat these remove and re-run steps till all covariates have 2-sided p-values < 0.05.
- (3) Forward selection procedure was utilized on all covariates not included from the univariate models or eliminated from the backwards elimination procedure: run the initial model including all covariates selected from the backward selection procedure, add to the initial model a covariate that was excluded at the univariate modeling and backward selection stages, re-run the model with the covariate identified, the covariate stays in the model from now if 2-sided p < 0.05 (otherwise removed) and repeat these and re-run steps till all previously excluded covariates have been tested.

A Cox proportional hazards model was fitted for OS in the similar fashion. A logistic regression model was fitted for ORR and PSA response in a similar fashion.

Analysis results regarding the association of each quantitative imaging variable in each anatomical and whole body region with each clinical outcome is summarized in Table 29.

Table 29. Quantitative Analysis Result Summary

Anatomic Region	Variable	rPFS	OS	ORR	PSA
Whole body	SUV _{mean}	S+	S+	S+	S+
	SUV _{max}			S-	
	Tumor volume				
	Tumor load	S-	S-		
	Presence of PSMA+ lesion in the bones	S+	S+	S+	
	Presence of PSMA+ lesion in the liver	S+	S+	S+	S+
	Presence of PSMA+ lesion in the lymph nodes		S+	S-	
Bone	Presence of PSMA+ lesion in the soft tissue				
	SUV _{mean}	S+	S+		S+
	SUV _{max}				
	Tumor volume		S-		
Liver	Tumor load	S-			
	SUV _{mean}				
	SUV _{max}				
	Tumor volume	S-	S-		
Lymph node	Tumor load				
	SUV _{mean}		S+	S+	
	SUV _{max}	S+			S+
	Tumor volume		S-	S+	
Soft tissue	Tumor load				
	SUV _{mean}				
	SUV _{max}	S+	S+	S+	S+
	Tumor volume		S-		
	Tumor load				

Source: Sponsor's Table 2.1 in Module 2.7.3 Summary of Clinical Efficacy Addendum

Blank = no statistically significant association observed

Abbreviations: ORR, objective response rate; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; S+, statistically significant association with improved clinical outcome; S-, statistically significant association with worse clinical outcome; SUV_{max}, maximum standardized uptake value; SUV_{mean}, mean standardized uptake value

Statistical Reviewer Comments:

This quantitative analysis was a planned analysis to study the association between the clinical outcomes (rPFS, OS, ORR, and PSA) and the aforementioned imaging data derived from GOZ PET scans of the VISION study but only in the investigational arm (VIP plus BSC/BSoC). The results of the quantitative analysis was verified by the statistical reviewer. This quantitative analysis is exploratory in nature due to the lack of the control arm data.

9.2. Conclusions and Recommendations

The review team recommends approval for Locametz, 111 MBq to 259 MBq (3 mCi to 7 mCi). Locametz is a radioactive diagnostic agent for PET imaging of PSMA-positive lesions in men with PC:

- With suspected metastasis who are candidates for initial definitive therapy.
- With suspected recurrence based on elevated serum PSA level
- For selection of patients with metastatic PC, for whom VIP PSMA-directed therapy is indicated.

10 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

An advisory committee meeting was not needed for this application.

11 Pediatrics

The Applicant's Position:

On 21-Jul-2020, Endocyte, Inc. received an Agreed Initial Pediatric Study Plan (iPSP) Agreement letter from the Agency, which included a full waiver of pediatric assessments in metastatic prostate cancer.

The FDA's Assessment:

The review team agrees that the approvable indications for Locametz are not applicable in the pediatric population.

12 Labeling Recommendations

The proposed prescribing information (PI) included three indications as follows:

“LOCAMETZ, after radiolabeling with gallium-68, is indicated 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 prostate-specific antigen (PSA) level.
- for (b) (4) of patients with metastatic prostate cancer, for whom PSMA-targeted therapy is indicated.”

The first two indications are the same as the approved indications in NDAs 212642 and 212643 (herein referred to as UCLA and UCSF, respectively). The two NDA PIs are identical except for manufacturer’s specific information: e.g., container size, fill volume, and expiration time.

The third indication is based on the VISION study where GOZ was used to select patients for treatment with lutetium Lu 177 vipivotide tetraxetan of which the marketing approval application was submitted under NDA 215833, Pluvicto.

The proposed PI consisted of the approved UCLA/UCSF PI plus information for the third indication. Most of labeling recommendations are for the third indication.

Highlights of labeling recommendations include the following:

- Indications and Usage

The specific therapeutic drug name “lutetium Lu 177 vipivotide tetraxetan” is added to the proposed third indication to parallel the Pluvicto PI which includes the following instruction in the Dosage and Administration section: “Select patients with previously treated mCRPC for treatment with PLUCVICTO using LOCAMETZ or another PSMA imaging agent based on PSMA expression in tumors.” The agreed third indication reads as:

“For selection of patients with metastatic prostate cancer, for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated.”

- Dosage and Administration

- Recommended Dosage (2.1): The recommended amount of radioactivity is the same as that of the UCLA/UCSF PI, 111 MBq to 259 MBq (3 mCi to 7 mCi), for all indications.
- Image Interpretation (2.8): The UCLA/UCSF PIs include instructions of how to determine and interpret positive lesions in the GOZ PET imaging. In addition to the instructions, the following specific selection criteria for VIP therapy are added based on findings from the VISION trial and VISION imaging studies:

“At least one tumor lesion is positive and all lesions on anatomical imaging larger in short axis than size criteria are also positive [size criteria: organs ≥ 1 cm, lymph nodes ≥ 2.5 cm, bones (soft tissue component) ≥ 1 cm].”

- The PI also includes recommendation of using the Locametz imaging in conjunction with other imaging modalities when Locametz is used to select patients for VIP therapy.
- Warnings and Precautions (5.1)
 - Risk for misinterpretation mirrors the UCLA/UCSF PI with regards to specificity of GOZ to prostate cancer, the serum level of PSA and Gleason score as variations for imaging performance, and the recommendation of histopathological evaluation of the suspected prostate cancer site.
 - Additionally, reader variability are added as a risk factor for misinterpretation in selecting patients for VIP therapy. The following recommendation for consistent reading is added:

“LOCAMETZ PET interpretations to select patients for lutetium Lu 177 vipivotide tetraxetan therapy may be more consistent when judging gallium Ga 68 gozetotide uptake in any one tumor lesion compared to judging uptake for all lesions larger than size criteria [see *Clinical Studies (14.3)*]. Multidisciplinary consultation to select patients for lutetium Lu 177 vipivotide tetraxetan therapy is recommended, particularly for LOCAMETZ imaging that a single reader finds borderline or difficult to interpret, or when patient eligibility hinges only on judgment of gallium Ga 68 gozetotide uptake for all lesions larger than size criteria.”
- Adverse Reactions (6.1)
 - The proposed labeling included safety data from the VISION study conducted to support the third indication. Adverse reactions reported at $\geq 0.5\%$ from the VISION study are presented in a table and adverse reactions reported $<0.5\%$ are listed separately to be consistent with the FDA regulation 21 CFR 201.57(c)(7) *6 Adverse reactions* and guidance “Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Contents and Format.”
 - In order to meet the FDA regulations requiring the entire safety database supporting all the claimed indications, safety information from the UCLA/UCSF PI is added. However, the safety data for the UCLA/UCSF studies are presented as a stand-alone with a linkage statement to clarify the source of information.
- Use in Specific Populations (8.5)
 - The Geriatric Use subsection (8.5) was proposed based on the VISION study only.
 - The study results for geriatric patients from the UCLA/UCSF studies are added to support all the claimed indications.
 - (b) (4)
and the following subsentence is added “other reported clinical experience has not identified differences in responses between the elderly and younger patients” to reflect the larger number of younger adult patients as a result of summation of the three studies and clinical use of the UCLA/UCSF products since its approval.

13 Postmarketing Requirements and Commitment

The Applicant agreed to a PMC related to the VISION study exploring imaging and outcomes. Refer to Section 8.1.2 for review. See also FDA's Multi-disciplinary Review and Evaluation for Pluvicto (NDA 215833) regarding PMC for patients with advanced/metastatic PC who had at least one PSMA-expressing tumor but did not meet the selection criteria used in VISION.

14 Division Director (Clinical)

I concur with the unanimous recommendation by the NDA review team for the approval of this 505(b)(2) application.

I concur that the comparative biopharmaceutical assessment, the comparative in vitro cell binding affinity and cellular internalization study in PSMA-expressing cell lines, and the comparison of mass dose and imaging performance in patients evaluated for radioligand therapy, provide adequate bridging between Locametz and the listed drug product. Therefore, the Applicant may rely on FDA's findings of effectiveness for the listed drug product (Ga 68 gozetotide injection under NDAs 2126642 and 212643) for two disease-detection indications. Namely, positron emission tomography of prostate-specific membrane antigen (PSMA)-positive lesions in men with prostate cancer: 1) with suspected metastasis who are candidates for initial definitive therapy, and 2) with suspected recurrence based on elevated serum prostate-specific antigen level.

I concur with the assessment that the effectiveness of Locametz for the third indication (namely, to select patients with metastatic prostate cancer for whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated) is demonstrated by the data from the VISION Study and the VISION Reviewer Variability Sub-study. In addition, the data from the VISION Quantitative Analysis Study provide supportive evidence for the patient selection effectiveness of Locametz. Finally, the diagnostic performance of Ga 68 gozetotide for the related disease-detection indications is considered supportive.

The VISION study demonstrated a statistically significant improvement in the efficacy outcomes of overall survival and radiographic progression-free survival in the Lu 177 vipivotide plus best standard care group compared to the group treated with best standard care alone. Therefore, the VISION Study showed the clinical utility of Ga 68 gozetotide PET scans for determination of patient eligibility to PSMA-targeted therapy with Lu 177 vipivotide.

The VISION Sub-study demonstrated acceptable (in the moderate range) reliability of Ga 68 gozetotide for patient selection based on assessment of the level of agreement between blinded reader assessments of PSMA status. The Warnings and Precautions section of the prescribing information cites the risk of misinterpretation of PSMA status and proposes risk mitigation strategies.

The Vision Quantitative Study provided support for the reliability of Ga 68 gozetotide because in the investigational treatment group for a preponderance of quantitative associations explored between imaging and treatment outcomes, measures of higher baseline PET signal, in general and mean standardized uptake values in particular, were associated with improved clinical response to treatment.

I concur that the safety profile of Locametz is acceptable. I concur with the review team's recommendation of the use of a flat dose of Ga 68 gozetotide consistent with the recommended dose for the listed drug product.

15 Appendices

15.1. References

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15.2. 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.

No concerns 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 to review safety and efficacy data during the course of the study.

Additionally, no site with investigators who disclosed financial interests/arrangements 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.

The FDA's Assessment:

The team has identified no review issues with the Applicant's position in this section.

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): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
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: <u>0</u> Significant payments of other sorts: <u>1</u>		

Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>4</u>		
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) <u>5</u>		
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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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