CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214032Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	NDA 214032
Priority or Standard	Standard
Submit Date	September 23, 2020
Received Date	September 23, 2020
PDUFA Goal Date	December 23, 2021
Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine (DIRM/OSM)
Review Completion Date	December 16, 2021
Established/Proper Name	Kit for the preparation of gallium Ga 68 gozetotide injection
Trade Name	ILLUCCIX
Pharmacologic Class	Radioactive diagnostic agent
Applicant	Telix Pharmaceuticals (US) Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	Target dose of (b) (4) MBq ((b) (4) mCi), with a range of (b) (4) MBq to (b) (4) MBq ((b) (4) mCi to (b) (4) mCi), as a bolus intravenous injection
Applicant Proposed Indication/Population	ILLUCCIX, after radiolabeling with Ga 68, is a radioactive diagnostic agent (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	461511000124101 -Biochemically recurrent prostate cancer (disorder)
Regulatory Action	Approval
Recommended Indication/Population	ILLUCCIX, after radiolabeling with Ga 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.
SNOMED CT Indication Disease Term	254900004 Carcinoma of prostate (disorder)
Recommended Dosing Regimen	111 MBq to 259 MBq (3 mCi to 7 mCi) as a bolus intravenous injection

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DIRM=Division of Imaging and Radiation Medicine

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Signatures

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
CDR	correct detection rate
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CT	computed tomography
ECG	electrocardiogram
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PET	positron emission tomography
PK	pharmacokinetics
PPV	positive predictive value
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
RLD	reference listed drug
SAE	serious adverse event
SUV_{max}	maximum standardized uptake value
TP	true positive
VLR	verified localization rate

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1 Executive Summary

1.1. Product Introduction

Gallium Ga 68 gozetotide injection (referred to as Ga 68 gozetotide in this review) is a peptide-based, positron-emitting radiopharmaceutical that binds to prostate-specific membrane antigen (PSMA), a protein that is overexpressed in most prostate cancers. Gozetotide is also known as PSMA-11. The current product, proprietary name ILLUCCIX, is a kit for the preparation of Ga 68 gozetotide containing non-radioactive ingredients that are radiolabeled with gallium 68 (Ga 68) at or near the site of clinical use to prepare the finished intravenous injection. Since the time of FDA receipt of this application, finished radiolabeled injection formulations (rather than kits) of the identical active ingredient, Ga 68 gozetotide, have been approved for production at University of California Los Angeles (NDA 212642) and University of California San Francisco (NDA 212643). Of note, while the active ingredient of these approved products is referred to as Ga 68 PSMA-11 in their respective NDA reviews and current labeling, it will be referred to as the synonymous Ga 68 gozetotide in this review.

NDA 214032 for the Applicant's kit was submitted under the 505(b)(2) pathway with proposed reliance on FDA's previous findings of safety and effectiveness for Ga 68 gozetotide injection under NDA 212643 as the reference listed drug (RLD). The recommended indications for Ga 68 gozetotide prepared by the Applicant's kit are the same as those of the approved injection formulations, namely positron emission tomography (PET) of PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or who have suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. Recommended intravenous dosing of 3 mCi to 7 mCi is also the same as that of the approved injection formulations.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness to support approval of the Applicant's kit was derived through reliance on the RLD, Ga 68 gozetotide injection under NDA 212643, for imaging of prostate cancer in two populations: 1) men with suspected metastasis who are candidates for initial definitive therapy, and 2) men with suspected recurrence based on elevated serum PSA. Reliance on the RLD was supported by bridging to the Applicant's kit through a combination of in vitro and clinical data along with a biopharmaceutical analysis of the formulations.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In American men, prostate cancer is the most common malignancy and the second-most common cause of cancer death. While many imaging techniques have been applied to prostate cancer, none have optimal performance. The need for improved prostate cancer imaging is reflected in the recurrence rate of up to 30% after definitive therapy of what was thought to be localized disease. Similarly, many patients with biochemical recurrence fail to have their disease localized by imaging. Diagnostic challenges persist despite recent imaging advances, such as multiparametric magnetic resonance imaging (MRI) and positron emission tomography (PET) drugs approved for prostate cancer, such as ^{18}F-fluciclovine.

Ga 68 gozetotide is a positron emitting radiopharmaceutical proposed by the Applicant for use with PET for the evaluation of prostate cancer. The Applicant seeks approval for a kit for the preparation of Ga 68 gozetotide injection based on FDA's findings of safety and effectiveness for the reference listed drug (RLD), Ga 68 gozetotide injection under NDA 212643. Reference is made to the previous FDA multi-disciplinary review for NDA 212643 dated November 11, 2020.

In patients with intermediate- to high-risk prostate cancer who are candidates for prostatectomy, the RLD showed low sensitivity but high specificity for Ga 68 gozetotide PET detection of pelvic lymph node metastases. Of note, there is reason to suspect that diagnostic performance of the RLD was underestimated due to trial design and conduct. The RLD data also suggest that Ga 68 gozetotide PET performs better in patients with higher grade prostate cancer in this setting. Regardless, it is anticipated that many patients with pelvic lymph node metastases will not be detected by Ga 68 gozetotide PET. However, given similar limitations in available imaging techniques, such false negative results are expected to have no impact on the treatment plan of definitive therapy in affected patients. The potential value of Ga 68 gozetotide PET lies in the demonstration that positive predictive value (PPV) exceeds the expected prevalence of lymph node metastasis in the population of intended use. While a positive PET scan may still need to be confirmed by other means, the results would allow a patient with metastasis to avoid the morbidity of surgery for more appropriate treatment. A positive PET scan might also help target therapy as part of the emerging paradigm of treatment of patients with limited metastases, also referred to as oligometastatic disease.

In patients with biochemical recurrence, the RLD data show favorable performance of Ga 68 gozetotide PET. Although traditional evaluation of sensitivity and specificity were precluded by the disease condition and trial design, the PPV results demonstrate that PET positive lesions are highly likely to be prostate cancer. Additionally, Ga 68 gozetotide PET displays good detection of lesions at

lower, more clinically meaningful prostate-specific antigen (PSA) levels. Such imaging qualities have the potential to positively impact patient care in this clinical setting where detection and localization of disease are critical.

The diagnostic performance of Ga 68 gozetotide PET in patients with biochemical recurrence supports the performance in patients who are candidates for definitive therapy of primary tumor, and vice versa.

For the safety evaluation, the RLD safety data were supplemented with adverse event data from 628 patients with prostate cancer who received Ga 68 gozetotide produced using the Applicant's kit. No new safety signal was identified. Treatment-emergent adverse events were uncommon. Radiation effective dose from Ga 68 gozetotide is typical of PET oncology imaging and estimated to impart minimal risk. Risk of misdiagnosis related to false negative and false positive results is applicable to imaging tests in general.

In summary, the benefit of Ga 68 gozetotide PET in the indicated patient populations with prostate cancer outweighs the acceptably low risks. Therefore, approval of this application is warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prostate cancer is the most common cancer in American men and the second most common cause of cancer related death in this population. • The course of prostate cancer 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 initial metastasis of prostate cancer. • Proper management of prostate cancer involves assessment of the risk of aggressive disease as well as evaluation of the location and extent of disease.	• Prostate cancer is a serious condition that causes substantial morbidity and mortality. • Imaging of disease can have important impact on patient management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Many imaging techniques have been applied to prostate cancer, including ultrasound, computed tomography (CT), MRI, bone imaging using Tc 99m medronate or F 18 fluoride, In 111 capromab pendetide single photon emission computed tomography, and PET using C 11 choline, F 18 fluciclovine, Ga 68 gozetotide, or F 18 piflufolastat. The technique used varies depending on what information is needed. • For patients with newly diagnosed prostate cancer 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 prostate cancer 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 the prostate gland is missed by traditional conventional imaging techniques in a number of cases. • Prostate cancer 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, Ga 68 gozetotide, and F 18 piflufolastat might also be used as they are specifically approved for prostate cancer imaging in the setting of biochemical	• Despite the availability of many different techniques for imaging prostate cancer, there is a 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 F 18 fluoride. • C 11 choline and F 18 fluciclovine are PET drugs approved specifically for imaging of prostate cancer in patients with biochemical recurrence. Lesion detection rates with these agents are limited at the low PSA levels of early recurrence. • Ga 68 gozetotide injection and F 18 piflufolastat are prostate-specific membrane antigen (PSMA)-specific PET drugs recently approved for use in the initial therapy and biochemical recurrence settings.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recurrence. There is a desire for higher detection rate when the PSA level is low.	
Benefit	• The Applicant is relying on FDA's finding of effectiveness for the RLD, Ga 68 gozetotide injection under NDA 212643. • There are differences between the Applicant's kit product and the RLD, including the ratio of Ga 68 gozetotide diastereomers and the maximum dose of gozetotide that can be administered. • Sources of bridging information between the Applicant's kit and the RLD included comparative biopharmaceutical analysis of the formulations, comparative in vitro cell binding and internalization data, a small comparative clinical pharmacology study, and analysis of PET positivity in patients receiving a range of mass doses of the drug.	• A bridge between the Applicant's kit and the RLD was established. • Substantial evidence of effectiveness was previously provided for the RLD, as detailed in the multi-disciplinary review for NDA 212643 dated November 23, 2020. • Approval of the Applicant's kit is expected to increase geographic availability of PSMA-specific PET.
Risk and Risk Management	• The Applicant is relying on FDA's finding of safety for the RLD. • Although the Applicant's kit has a higher allowable maximum mass dose of gozetotide than the RLD, it remains a microdose product. No new safety signal was identified in the Applicant's development program, which included clinical exposures of relevant higher mass doses. • The radiation effective dose is estimated to be 4.4 mSv for a 7 mCi administered dose.	• No safety concerns were identified. • The radiation effective dose of Ga 68 gozetotide is typical of oncologic PET imaging.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	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		
	☐	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 were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application and is not needed.**			

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2 Therapeutic Context

2.1. Analysis of Condition

The American Cancer Society estimated that in 2021, prostate cancer will be the most commonly diagnosed cancer in American men, with 248,530 new cases predicted ("Cancer Statistics Center," 2021). While prostate cancer-specific mortality has decreased over recent history, by 51% from 1993 to 2016, prostate cancer is predicted to be the second most common cause of cancer-induced fatality in men in 2021, with 34,130 deaths predicted. Also, in recent years there has been a trend toward diagnosis of prostate cancer at higher stages, which is presumably due to changes in prostate cancer screening practices. These statistics demonstrate the need for continued advances in prostate cancer diagnosis and therapy.

The large majority of prostate cancers are carcinomas of two broad types, glandular and neuroendocrine (Humphrey, 2017). The most common prostate cancer overall is a glandular type, acinar adenocarcinoma, although another glandular type, intraductal carcinoma, may often coexist with it and suggests a more aggressive course (Humphrey, 2017). While less common, the neuroendocrine carcinomas of the prostate are important to recognize as they are treated differently. One of these, small cell carcinoma, is notable for its propensity to arise after treatment of acinar adenocarcinoma, accounting for about of one of three patients with small cell carcinoma of the prostate.

The natural history of prostate cancer is variable, ranging from indolent tumors that remain confined to the prostate for decades to highly aggressive tumors that rapidly metastasize and lead to death. Accordingly, it is necessary to predict the aggressiveness of the cancer at diagnosis to determine management and prevent undertreatment or overtreatment. Typically, a panel of risk factors is evaluated, but because there are many contributory factors, several methods have been devised. One of the earliest was the D'Amico risk classification, which includes the tumor stage by the American Joint Committee on Cancer TNM criteria (T: primary tumor features, N: involvement of regional lymph nodes, and M: the presence or absence of distant metastases), tumor grade by Gleason score, and serum level of PSA and divides patients into low-, intermediate-, and high-risk categories (D'Amico et al., 1998). The widely used National Comprehensive Cancer Network classification (Mohler et al., 2019) includes additional information from the prostate biopsy, such as the number of positive cores and PSA density, to generate six risk categories. Most risk stratification schemes do not explicitly incorporate imaging, with the goal of minimizing unnecessary testing procedures and associated expense. Instead, imaging of patients with newly diagnosed prostate cancer is performed once a risk threshold has been passed.

As with most other malignancies, prostate cancer can metastasize throughout the body and very often follows typical pathways of progression. Prostate cancer is most likely to spread initially to the pelvic lymph nodes, including the obturator, internal iliac, and external iliac

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chains. These sites are designated regional metastases. Once beyond the pelvic lymph nodes, the abdominal retroperitoneal lymph nodes and bones are the most common locations of metastasis. More advanced patterns of tumor progression can involve extrapelvic, non-nodal soft tissue sites like liver and lung.

For prostate cancer localized to the prostate gland, if the risk of progression is considered high enough, curative intent therapy using radical prostatectomy or radiation therapy has good success rates (Mohler et al., 2019). After definitive therapy, the patient's PSA level should fall and become undetectable in the case of prostatectomy or reach a nadir in the case of radiotherapy. Monitoring for recurrence largely focuses on a combination of clinical signs and symptoms as well as serum PSA level. A rising PSA level after definitive therapy indicates a very high likelihood that prostate cancer is present and is termed biochemical recurrence (Roach et al., 2006; Cookson et al., 2007). Current treatment in this situation is typically non-curative in intent, but optimal management still depends on knowledge of disease location and extent. In addition, localized therapies such as radiotherapy or percutaneous ablative techniques are being tested on oligometastatic prostate cancer in initial and recurrent settings, and precise localization of disease could further facilitate effective therapy in such a setting.

Ga 68 gozetotide allows PET imaging of prostate cancer through binding to the PSMA. This molecule, also known as glutamate carboxypeptidase II or folate hydrolase I, is a transmembrane protein with an extracellular enzymatic domain. PSMA is expressed in normal prostate epithelial cells where its function is unknown (Silver et al., 1997; Bostwick et al., 1998). PSMA is also expressed in other normal tissues, particularly the glia of the central nervous system where it is involved in glutaminergic neurotransmission, the renal proximal tubules, in breast epithelium, and in the gut where it may be involved with folate uptake.

In the majority of prostate adenocarcinomas, PSMA is overexpressed compared to benign prostate epithelium. For example PSMA was overexpressed in 33 of 35 tumor specimens in one case series (Silver et al., 1997). PSMA also appears to be more highly expressed in higher grade tumors (Bravaccini et al., 2018). However, neuroendocrine prostate cancer, particularly when it arises after treatment of prostate adenocarcinoma, may have low or absent PSMA expression. PSMA expression is also less common in bone metastases than in the primary prostate tumor (Silver et al., 1997).

The term prostate-specific membrane antigen is somewhat misleading as there are many literature reports of PSMA overexpression in certain non-prostate malignancies and non-malignant conditions. For many malignancies, this effect may be mediated by expression of PSMA in the neovasculature rather than in malignant cells (Chang et al., 1999). This phenomenon has been reported in several cancers, including non-small cell lung cancer, melanoma, colon cancer, clear cell renal cell carcinoma, and thyroid carcinoma. In certain case series, PSMA expression results in visualization of non-prostate cancers on Ga 68 gozetotide PET (Salas Fragomeni et al., 2018). Similarly, benign tumors such as thyroid adenoma and hemangioma (soft tissue and bone) may be visualized by Ga 68 gozetotide PET. Normal

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osteoblasts express PSMA, and this observation may explain the increased uptake of Ga 68 gozetotide in a variety of benign bone diseases such as Paget disease, fibrous dysplasia, osteoarthritis, and fracture (Hofman et al., 2018).

2.2. Analysis of Current Treatment Options

The use and effectiveness of imaging in patients with prostate cancer varies with the task to be accomplished. Imaging options are summarized in Table 1. Note that several of these options are not specifically approved for prostate cancer imaging and that imaging is not recommended for prostate cancer screening.

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 ^{99m}Tc-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

Technique	Use in Practice	Performance Estimates	Comments
C 11 choline	Restaging	Identifying disease after BCR: PPV 82%	Approved for PET imaging of prostate 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 of prostate cancer only in the BCR setting
Ga 68 gozetotide (Ga 68 PSMA-11) injection	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 47% Specificity 90% Identifying disease after BCR: PPV 91%	PSMA-targeted Very limited geographic availability of the approved products at this time
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

Sources: (Leventis et al., 2001; Heck et al., 2014; Poulsen et al., 2014; Mohler et al., 2019), labels for In 111 capromab pendetide, C 11 choline, F 18 fluciclovine, Ga 68 PSMA-11 injection, and F 18 piflufolastat.
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, RP = radical prostatectomy, SPECT = single photon emission computed tomography

The diagnostic yield of these tests depends on the likelihood that unknown disease is present in the imaged area. Therefore, imaging is usually restricted to patients with higher risk disease. This dependence also explains some of the variability in the reported test performance results; estimates in Table 1 are from selected publications, or where available from the approved labeling. While reliable within-study comparisons of different imaging agents and modalities are generally unavailable, it can be summarized that traditional imaging techniques have less than optimal performance for detection of prostate cancer, particularly in clinically meaningful situations where tumor lesions are small in volume.

As a non-radioactive kit, approval of the Applicant's product is expected to enhance geographic availability of PSMA-specific PET by allowing sites with appropriate generator or cyclotron sources of Ga 68 to locally radiolabel Ga 68 gozetotide for clinical use.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

When this application was submitted and filed, Ga 68 gozetotide was a new molecular entity and was not marketed in the United States. During review of this application, Ga 68 gozetotide was approved in injection formulations under NDA 212642 and NDA 212643, both on December 1, 2020. Thus, at the time of this review, Ga 68 gozetotide was no longer considered a new molecular entity. A kit for preparation of Ga 68 gozetotide has not been previously approved or marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

On May 21, 2019, FDA received a pre-NDA meeting request from the Applicant to discuss their development plan for a kit for preparation of Ga 68 gozetotide injection under IND 144421. During this meeting, FDA advised the Applicant that an adequate and well-controlled prospective study should be performed to address gaps in the evidence of safety and effectiveness present in the scientific literature.

The Applicant requested an additional written response only meeting on December 24, 2019, to obtain comment on the synopsis of their planned phase 3 efficacy study. Multiple comments were provided related to study design and FDA recommended submission of the complete protocol with another written response only meeting request to provide additional review and comment.

NDA 214032 for a kit for the preparation of Ga 68 gozetotide injection was received on September 23, 2020, as a 505(b)(2) application relying in part on published scientific literature. The application was filed on November 22, 2020, with a standard review timeline (12 months).

On March 10, 2021, the Applicant updated their application to rely on FDA's findings of safety and effectiveness for Ga 68 PSMA-11 injection approved under NDA 212643.
Additional product quality information requested during NDA review was received on September 20, 2021 and was determined to constitute a major amendment to the application. Therefore, the standard review timeline was extended by an additional three months to allow full review of the submissions.

Chemistry, manufacturing, and controls (CMC) and Microbiology postmarketing commitments (PMCs) were communicated to the Applicant on November 08, 2021, to provide additional data. The Applicant responded on November 12, 2021, and agreed to provide the requested data by February 28, 2022, and April 29, 2022, respectively.

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

4.1. Office of Scientific Investigations

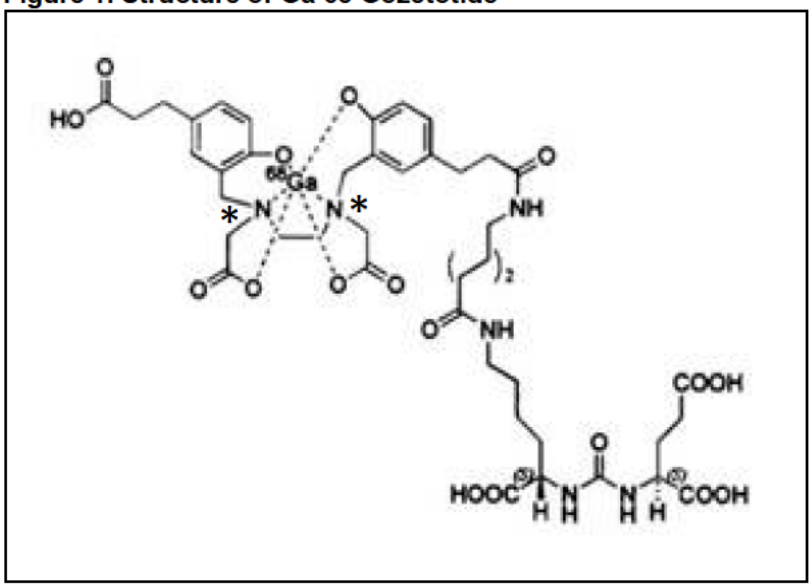
No Office of Scientific Investigation audit was requested for this application that relied on clinical data from the previously audited NDA 212643.

4.2. Product Quality

Reference is made to the separate Integrated Quality Assessment dated December 16, 2021.

The drug product, Ga 68 gozetotide injection, is prepared from a kit which contains the drug product precursor gozetotide (25 µg), as well as the excipients D-mannose (10 µg) and sodium acetate (150 mg). The drug product is a sterile, clear, pyrogen free, colorless aqueous solution and is presented in a multiple-dose vial. The structure of Ga 68 gozetotide is shown in Figure 1.

Figure 1. Structure of Ga 68 Gozetotide



Source: Ga 68 PSMA-11 injection prescribing information
Note: * indicates the chiral centers of the metal chelating moiety of the drug.

The radiolabeling process is conducted using Ga 68 chloride solution from an Eckert and Ziegler GalliaPharm, IRE Galli Eo Ge 68/Ga 68 generator or from cyclotron source, and a cGMP gozetotide (also known as PSMA-11) precursor supplied by a commercial supplier (b) (4) (b) (4)

The product met all the drug product and microbiological quality regulatory specifications. Stability data provided supported the proposed 4-hour expiration.

The Agency's preapproval inspection of the Applicant's kit product manufacturing facility at GRAM identified deficiencies in analytical methodology and process controls. The Agency notified the Applicant that there were insufficient data in the application to assess the lyophilized gozetotide. The Agency requested additional data regarding (b) (4) not previously submitted in the original application. Data received on September 20, 2021, constituted a major amendment to the Application. Additionally, CMC and Microbiology PMCs were communicated to the Applicant on November 08, 2021, to improve the method (b) (4) and sterility of the Ga 68 gozetotide produced from aged generator eluates. The Applicant agreed to the PMCs on November 12, 2021, and agreed to provide the requested data by February 28, 2022, and April 29, 2022, respectively.

4.3. Clinical Microbiology

This section is not applicable to this NDA.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable to this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ga 68 gozetotide is a microdose product with a clinical mass dose of not more than 25 µg. This dose is sub-pharmacologic, and therefore certain nonclinical data for such an application are not needed, as described in the FDA guidance document, "Microdose Radiopharmaceutical Diagnostic Drugs: Nonclinical Study Recommendations" (https:www.fda.gov/media/107641/download). Nonclinical studies to evaluate absorption, distribution, metabolism, excretion/ pharmacokinetics, genetic toxicology, carcinogenicity, and reproductive and developmental toxicology are not typically required for microdose radiopharmaceutical applications and none were submitted to the NDA.

The Applicant submitted one nonclinical pharmacology study report (ANMI-PG01-NC01) and an expanded single-dose rat intravenous toxicity study. No adverse effects were observed with a dose of 86 µg/kg gozetotide, a 33-fold safety factor over the 25 µg maximum clinical mass dose based on human equivalent dose calculations.

While these studies provide sufficient nonclinical data to support approval of the NDA, study ANMI-PG01-NC01 is also a supportive component of the bridge between the Applicant's kit and Ga 68 gozetotide injection approved under NDA 212643, the RLD upon which the Applicant proposes reliance for evidence of safety and effectiveness. This study addresses a bridging issue

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related to the three diastereomers (R,R; R,S; and S,S configurations) Ga 68 gozetotide can form during Ga complexation. The Ga 68 gozetotide synthesis method used by the Applicant results in a (b) (4) percentage of the R,R configuration and a (b) (4) percentage of the R,S configuration compared to the synthesis methods that were approved for the RLD.

In study ANMI-PG01-NC01, the Applicant demonstrated that Ga 68 gozetotide prepared with a method analogous to the RLD that contained over (b) (4)% R,R configuration at the end of synthesis had similar binding and internalization to PSMA-expressing cells in vitro compared to Ga 68 gozetotide prepared with the Applicant's kit that contained under (b) (4)% R,R configuration and over (b) (4)% R,S configuration at the end of synthesis. As such, this study contributes to the bridge between the Applicant's kit and the RLD, as further discussed in Section 6 of this review.

The nonclinical review discipline recommends approval of the application.

5.2. Referenced NDAs, BLAs, DMFs

As noted above, the Applicant proposes to rely on Ga 68 gozetotide injection approved under NDA 212643 as the RLD.

5.3. Pharmacology

The HBED-CC chelating moiety of Ga 68 gozetotide has two chiral centers at the amine nitrogens (see Figure 1 in Section 4.2 of this review), and upon complexation with gallium, there are three possible diastereomers: R,R; R,S; and S,S. Of these, R,R is thermodynamically favored. The initial distribution of diastereomers after gallium complexation depends on reaction conditions including temperature. Under the high temperature conditions used for synthesis of the RLD, about (b) (4)% of the Ga 68 gozetotide consists of the R,R diastereomer at the end of synthesis. In contrast, preparation of Ga 68 gozetotide with the Applicant's kit occurs at room temperature and results in approximately (b) (4)% R,R diastereomer at the end of synthesis.

Whether this difference in the ratio of diastereomers might impact drug affinity for PSMA was addressed by the Applicant in study ANMI-PG01-NC01. Of note, interconversion of the R,S and S,S diastereomers to the more stable R,R configuration occurs over time. As part of study ANMI-PG01-NC01, Ga 68 gozetotide prepared with the Applicant's kit was found to reach ~ (b) (4)%, ~ (b) (4)%, and ~ (b) (4)% R,R isomerization at 30, 60, and 120 minutes after the end of synthesis, respectively, while incubated in cell culture medium. These measurements were made using reversed phase high performance liquid chromatography equipped with a radiodetector.

In study ANMI-PG01-NC01, the Applicant also compared PMSA-specific cell binding and internalization in vitro between Ga 68 gozetotide prepared with the Applicant's kit containing a mixture of the R,R and R,S diastereomers (under (b) (4)% and over (b) (4)%, respectively) at the end of synthesis and Ga 68 gozetotide prepared through a high temperature (95°C) method analogous to the RLD containing over (b) (4)% R,R diastereomer. Ga 68 gozetotide preparations at 0 minutes, 30 minutes, 60 minutes, and 120 minutes of "resting time" from the end of synthesis were

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evaluated for binding and internalization using LNCaP cells (a human prostate cancer cell line that expresses PSMA) at 15 minutes, 30 minutes, 45 minutes, and 60 minutes following cell exposure. Such evaluation was conducted with and without the addition of 2-(phosphonomethyl)pentanedioic acid (2-PMPA), a specific inhibitor of PSMA, as a competitive blocking agent to demonstrate the degree of PMSA-specific uptake and internalization. Of note, viability of LNCaP cells was not significantly different from untreated cells for either Ga 68 gozetotide preparation. Results for both Ga 68 gozetotide preparations applied to LNCaP cells at the end of synthesis are displayed in Table 2.

Table 2. Binding and Internalization by LNCaP Cells of Ga 68 Gozetotide Prepared by the Applicant's Kit (Telix) and the RLD Method (Heated) at the End of Synthesis

Cell Line	Sample	% Injected Dose	
		Telix	Heated[1]
LNCaP	Binding at 15 minutes	1.051	0.950
	Binding at 15 minutes + 2-PMPA	0.436	0.341
	Internalization at 15 minutes	0.077	0.085
	Internalization at 15 minutes + 2-PMPA	0.031	0.031
	Binding at 30 minutes	0.929	0.834
	Binding at 30 minutes + 2-PMPA	0.437	0.203
	Internalization at 30 minutes	0.086	0.141
	Internalization at 30 minutes + 2-PMPA	0.037	0.034
	Binding at 45 minutes	0.575	0.928
	Binding at 45 minutes + 2-PMPA	0.219	0.341
	Internalization at 45 minutes	0.110	0.222
	Internalization at 45 minutes + 2-PMPA	0.012	0.052
	Binding at 60 minutes	0.635	0.970
	Binding at 60 minutes + 2-PMPA	0.184	0.219
	Internalization at 60 minutes	0.127	0.309
	Internalization at 60 minutes + 2-PMPA	0.022	0.057

Source = Adapted from Table 4 of 2.6.2 Pharmacology Written Summary
1 = Heated is Ga 68 gozetotide prepared at 95°C using a method analogous the RLD

As shown in Table 2, comparable levels of binding and internalization by LNCaP cells were demonstrated for both Ga 68 gozetotide preparations applied at the end of synthesis when considering experimental error. Additionally, similar levels of inhibition of cell binding and internalization by 2-PMPA for both Ga 68 gozetotide preparations demonstrated a comparable degree of PSMA-specificity.

Binding and internalization by LNCaP cells were also similar for both Ga 68 gozetotide preparations with resting for 30 minutes, 60 minutes, or 120 minutes after the end of synthesis before application to cells. Parallel control experiments with PC-3 cells, a human prostate

cancer cell line that does not express PSMA, demonstrated similar low levels of binding and internalization for both Ga 68 gozetotide preparations.

Overall, the results of study ANMI-PG01-NC01 demonstrate that the difference in the ratio of diastereomers for Ga 68 gozetotide prepared with the Applicant's kit and the RLD does not appear to impact drug affinity for PSMA.

For additional nonclinical pharmacology information pertinent to Ga 68 gozetotide, including published data gathered through studies conducted in vitro and in a xenograft tumor mouse model, refer to Section 5.3 of the multi-disciplinary review for NDA 212643 dated November 23, 2020.

5.4. ADME/PK

Refer to Section 5.3 of the multi-disciplinary review for NDA 212643 dated November 23, 2020, for additional information.

5.5. Toxicology

5.5.1. General Toxicology

No adverse effects were observed in a rat expanded single-dose intravenous toxicity study using a dose of 86 µg/kg gozetotide (referred to in the study report as PSMA (HBED)), providing a 33-fold safety factor over the 25 µg maximum clinical mass dose based on human equivalent dose calculations.

Study Title/ Number: Extended Single-Dose Toxicity Study of PSMA (HBED) Administered Intravenously in Male and Female Wistar Rats (Study # 770.321.4369)

- No drug-related adverse effects were observed in this study.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods	
Dose and frequency of dosing:	Single-dose of 0 or 86 µg/kg (Day 1)
Route of administration:	Intravenous
Formulation/Vehicle:	Solution/Phosphate-Buffered Saline
Species/Strain:	Rat/Wistar
Number/Sex/Group:	10/sex/group main study (euthanized on Day 2) and 5/sex/group recovery (euthanized on Day 15)
Age:	~7 weeks at initiation of dosing.
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None

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Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical Signs	No drug-related clinical signs noted.
Body Weights	No drug-related effects on body weights.
Hematology	Mean hematocrit was significantly increased (by ~ 3% relative to control) in the main study treated male group. However, the magnitude of change was too small to be considered adverse.
Clinical Chemistry	Mean total protein was significantly increased (by ~ 5% relative to control) and mean albumin/globulin ratio was significantly decreased (by ~ 8% relative to control) in the main study treated male group. However, the magnitude of change was too small to be considered adverse.
Gross Pathology	No drug-related adverse macroscopic findings.
Organ Weights	Mean absolute and relative ovaries and uterus weights were decreased by ~ 20% in the recovery treated female group compared to the control groups. These findings were not considered adverse as they were not correlated with any microscopic findings.
Histopathology Adequate battery: Yes	No drug-related adverse microscopic findings
Other Evaluations	No drug-related effects on feed consumption.

Also refer to Section 5.5.1 of the multi-disciplinary review for NDA 212643 dated November 23, 2020, for additional general toxicology information.

General Toxicology; Additional Studies

Not conducted and not needed.

5.5.2. Genetic Toxicology

Not required for a microdose and single use product.

5.5.3. Carcinogenicity

Not required for a single use product.

5.5.4. Reproductive and Developmental Toxicology

Not conducted. The Applicant requested and was granted a waiver from conducting the studies.

5.5.5. Other Toxicology Studies

Not conducted and not needed.

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6 Clinical Pharmacology

6.1. Executive Summary

The Applicant proposes reliance on Ga 68 gozetotide injection approved under NDA 212643 in December 2020 as a RLD. Since the amount of active and inactive ingredients are not the same in the ILLUCCIX and RLD drug products, consultation with the Division of Biopharmaceutics in the Office of New Drug Products concluded that a biowaiver was not applicable and that bridging needed to be established. While the Applicant's comparison of physiochemical properties between the products supported a scientific bridge from the biopharmaceutics perspective, other sources of bridging evidence were examined.

One source of bridging evidence consisted of a limited clinical pharmacology study (GA68PSMA-2016-1) conducted by the Applicant The study compared the pharmacokinetics, biodistribution, and dosimetry of Ga 68 gozetotide prepared by the Applicant's kit and the RLD method in three healthy subjects through a cross-over design. Although plasma time-activity curves, dosimetry data, and maximum standardized uptake value (SUV_{max}) measurements for major organs appeared similar between the formulations, the results of this small study alone were too limited to establish a definitive conclusion of equivalence.

Additional sources of bridging evidence focused on differences in the Applicant's kit and RLD drug product formulations that could theoretically impact efficacy. One notable difference is that gozetotide supplied in the Applicant's kit is (b) (4) whereas the RLD product uses (b) (4) method (b) (4) Reaction temperature affects the ratio of Ga 68 gozetotide diastereomers. To address the potential of any related impact on drug targeting, the Applicant conducted an in vitro cell binding and internalization study to compare Ga 68 gozetotide (b) (4) (b) (4) In vitro comparability was adequately demonstrated, as described in Section 5 of this review.

Another major difference in the Applicant's kit and RLD drug product formulations is the mass dose of gozetotide, the active pharmaceutical ingredient, per batch. Up to 25 µg of gozetotide can be delivered in a single patient dose using the Applicant's kit, whereas the RLD delivers a maximum of 5 µg of gozetotide per patient dose, or potentially 10 µg if two batches are pooled. An important aspect of "imaging bioequivalence" is to assess whether the amount of "cold" compound affects the clinical performance of the radiolabeled drug. As discussed in Section 7 of this review, analysis of the clinical data with the Applicant's kit demonstrated no effect of mass dose within a relevant range on imaging performance.

The above sources of evidence, including comparative biopharmaceutical assessment, the Applicant's in vitro binding/internalization study, evaluation of mass dose and imaging

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performance using the Applicant's clinical data, and the Applicant's clinical pharmacology study, together support adequate bridging between the Applicant's kit and the RLD product.

6.2. Summary of Clinical Pharmacology Assessment

The post-radiolabeling drug product formulations of ILLUCCIX and the RLD are detailed in Table 3, in which Ga 68 gozetotide is referred to as Ga-68 PSMA-11.

Table 3. Post-Radiolabeling Drug Product Formulations of ILLUCCIX and the RLD (Ga 68 Gozetotide is Referred to as Ga-68 PSMA-11)

	ILLUCCIX Kit for the Preparation of Ga-68 PSMA-11			UCSF Ga-68 PSMA-11 Reference Product (Cyclotron Based)			UCSF Ga-68 PSMA-11 Reference Product (Generator Based)		
Component	Quantity/ Vial	Function	Quality Standard	Quantity/ Vial	Function	Quality Standard	Quantity/ Vial	Function	Quality Standard
Ga-68 PSMA-11	Up to (b) (4) mCi/mL[1]	Drug substance	In-house	0.5–5 mCi/mL	Drug substance	In-house	0.5–5 mCi/mL	Drug substance	In-house
PSMA-11	25 µg[1]	Precursor	In-house	5 µg	Precursor	GMP	5 µg	Precursor	GMP
D-Mannose	10 µg	Stabilizer	In-house			(b) (4)			(b) (4)
Hydrochloric acid, (b) (4) M[2]	(b) (4) mL	(b) (4)	NF						
Hydrochloric acid, 1 M[2]			(b) (4)				5 mL	Generator eluent	GMP
Hydrochloric acid, 1.75 M[3]				4 mL	Ga-68 Purification	Ultrapure			(b) (4)
Sodium acetate, 0.5M[3]						(b) (4)	0.1 mL	Buffering agent	Pharma grade
Sodium acetate, 1M[3]				1.3 mL	Buffering agent	Pharma grade			(b) (4)
Sodium acetate, anhydrous	150 mg	Buffer	USP			(b) (4			
Nitric acid, 0.1 M[3]			(b) (4)	4 mL	Ga-68 purification	Trace metal basis			
Sodium Chloride, 2M[3]				4 mL	Ga-68 Purification	Trace metal basis			
Ethanol, 60%				1 mL	Product eluent	USP grade	1 mL	Product eluent	USP grade
Ultra-high purity water				50 mL	Solution preparation	Pharma grade	10 mL	Solution preparation	Pharma grade
Water for Injection USP				100 mL	Solution preparation	USP grade	4 mL	Solution preparation	USP grade
Sodium Chloride 0.9% Injection				5–10 mL	Isotonicity	USP grade	5–10 mL	Isotonicity	USP grade

[1] A part of the Drug Substance PSMA-11 has been radiolabeled with Gallium-68 to form Ga-68 PSMA-11.
[2] (b) (4)
[3] Removed during processing and not present in the final formulation of the UCSF Ga-68 PSMA-11 reference product.
(b) (4)

Source: Table 2 from Applicant's June 29, 2021, response to an information request
Abbreviations: RLD, reference listed drug

Per the biopharmaceutics review in the separate Integrated Quality Assessment dated December 16, 2021, and in accordance with CFR 320.22(b)(1), a drug product's in vivo bioequivalence may be considered self-evident if the product meets the following criteria: (1) the drug product (i) is a parenteral solution intended solely to be administered by injection and (ii) contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or ANDA. Since the amount of active and inactive ingredients are not in the same concentration in the ILLUCCIX and RLD drug product, biopharmaceutics review concluded that a biowaiver was not applicable and that bridging needed to be established.

As such, the Applicant demonstrated bridging/comparability of their product to the RLD through the following sources of evidence:

1. Comparison of physiochemical properties
2. Comparison of PSMA-specific cell binding and internalization in vitro
3. Evaluation of the relationship between mass dose and clinical imaging performance
4. Comparison of pharmacokinetics, biodistribution, and dosimetry in three healthy subjects

Regarding the first source of evidence listed above, biopharmaceutics review found physiochemical properties like pH, osmolality, and radiochemical purity to be similar or adequately controlled for ILLUCCIX and the RLD. As such, a scientific bridge between these products was supported from a biopharmaceutics perspective, with deference to other review disciplines for any concerns regarding differences in inactive ingredients, such as D-mannose and acetate. Nonclinical, clinical pharmacology, and clinical review disciplines had no concerns with the inactive ingredients.

Regarding the second and third sources of evidence listed above, in vitro binding and internalization data and evaluation of the relationship between mass dose and clinical imaging performance are discussed in Section 5 and Section 7.2 of this review, respectively. In brief, these evaluations also supported bridging between the Applicant's kit and the RLD product.

The fourth source of evidence listed above, the Applicant's clinical study that compared the pharmacokinetics, biodistribution, dosimetry of Ga 68 gozetotide prepared with the Applicant's kit and the RLD method, is described in detail below.

Comparative Pharmacokinetic Profile, Biodistribution, and Dosimetry (Study GA68PSMA-2016-1)

Ga 68 gozetotide was prepared with the Applicant's kit and the RLD method (b) (4) Three healthy subjects were administered 185 MBq (± 10% ; range 166.5 to 203.5 MBq) doses of each preparation in a cross-over study design. Plasma area under the time-concentration curve (AUC) and half-life are compared between Ga 68 gozetotide prepared with the Applicant's kit and the RLD method in Table 4.

Table 4. Mean Pharmacokinetic Parameters in Three Healthy Subjects Administered Ga 68 Gozetotide Prepared With the Applicant's Kit and the RLD Method in a Cross-Over Study

Ga 68 Gozetotide Preparation	Plasma AUC (%ID min/mL, mean ± SD)	Half-Life (min, mean ± SD)
Applicant's kit	2698 ± 210	155±29
RLD method	2607 ± 320	226±190

Source: Study Ga-68PSMA2016-1 (Table 4)
Abbreviations: AUC = area under the time-concentration curve, %ID = percent injected dose, min = minute, RLD = reference listed drug, SD = standard deviation

Plasma AUC values appeared consistent between products. Mean half-lives were similar, although extensive variability likely due to the small number of subjects precludes detailed evaluation.

Serial urine samples were measured in a gamma well-counter and activities were expressed as a percentage of the injected dose (%ID). Urinary excretion was measured as %ID over three intervals (0-50 min, 50-100 min and 100-180 min). The total mean radioactivity excreted in the urine by 180 minutes was 43% for the Applicant's kit and 37% for the RLD method preparation.

Per the Applicant, comparative biodistribution assessed visually on whole-body PET scans performed at 60 and 120 minutes post-injection was found to be similar between the preparations. Semiquantitative measurements of SUV_{max} in organs that had the highest uptake of radioactivity were also found to be comparable between preparations (Table 5).

Table 5. Mean SUV_{max} (Standard Deviation) in Organs With the Highest Uptake in Three Healthy Subjects Administered Ga 68 Gozetotide Prepared With the Applicant's Kit and the RLD Method in a Cross-Over Study

Organ	Applicant's Kit	RLD Method
Lacrimal gland	8.6 (4.7)	7.55(2.9)
Left kidney	36.2 (20.0)	41.5(16.3)
Right kidney	37.0 (18.8)	42.7 (16.6)
Left parotid gland	15.5 (4.5)	13.9 (1.7)
Right parotid gland	15.6 (2.2)	17.6 (5.8)
Left submandibular gland	17.6 (3.6)	17.1 (3.0)
Right submandibular gland	17.2 (2.8)	19.5 (5.2)
Liver	3.8 (1.0)	3.7 (0.4)
Prostate	3.0 (0.7)	2.7 (0.4)
Spleen	6.1 (1.7)	6.3 (1.8)

Source: Study Ga-68PSMA2016-1 (Table 5)
Abbreviations: RLD = reference listed drug, SUV_{max} = maximum standardized uptake value

Dosimetry data were also calculated on whole-body PET scans performed at 60 and 120 minutes post-injection with arms along the body. The source organs for dosimetry calculations included brain, right and left parotid glands, right and left submandibular glands, thyroid gland, heart, lungs, liver, spleen, right and left kidneys, pancreas, small bowel, colon, bone, bone marrow, and prostate gland. The true activities in all quantifiable organs (i.e., those that could be clearly delineated from other organs) were measured on attenuation- and scatter-corrected images, and organ volumes were measured by computed tomography (CT) imaging. Activities and volumes were processed with OLINDA/EXM software for determining absorbed doses (mGy/MBq) and effective doses (mSv/MBq).

For the Applicant's kit, resulting absorbed doses for individual organs were highest in the kidneys, urinary bladder wall, salivary glands, small bowel, spleen, and liver, listed in order of decreasing mean absorbed dose over a range of 0.46 to 0.022 mGy/MBq. Similar data were observed for the RLD method preparation, with the same ranking of organs with the highest absorbed dose over a range of 0.51 to 0.020 mGy/MBq. Table 6 displays mean absorbed doses for selected organs and effective doses calculated with each preparation.

Table 6. Dosimetry Data for Selected Organs in Three Healthy Subjects Administered Ga 68 Gozetotide Prepared With the Applicant's Kit and the RLD Method in a Cross-Over Study

Organ	Applicant's kit Absorbed Organ Dose (mGy/MBq, mean ± SD)	RLD method Absorbed Organ Dose (mGy/MBq, mean ± SD)
Kidneys	0.46 ± 0.22	0.51 ± 0.18
Salivary Glands	0.09 ± 0.05	0.10 ± 0.05
Spleen	0.04 ± 0.02	0.03 ± 0.02
Effective Dose (mSv/MBq)	**0.016 ± 0.003**	**0.017 ± 0.002**

Source: Applicant's data from Study Ga68PSMA-2016-1 (Table 16)
Abbreviations: RLD, reference listed drug, SD = standard deviation

When using the standard organ volumes described in OLINDA, effective dose was calculated to be 0.0190 mSv/MBq (standard deviation = 0.0015) for the Applicant's kit and 0.0194 mSv/MBq (standard deviation = 0.0019) for the RLD method preparation.

In summary, available limited pharmacokinetic, biodistribution, and dosimetry data appeared comparable for Ga 68 gozetotide prepared with the Applicant's kit and the RLD method, providing an additional component of support for bridging between these products.

6.2.1. Pharmacology and Clinical Pharmacokinetics

See above.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Dosing will be the same as that of the RLD (111 MBq to 259 MBq (3 mCi to 7 mCi) as a bolus intravenous injection).

Therapeutic Individualization

None.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

As described above, the Applicant's clinical study in three healthy subjects that compared pharmacokinetics, biodistribution, and dosimetry data using Ga 68 gozetotide prepared with the Applicant's kit and the RLD method in part supported a bridge for this 505(b)(2) application. For additional detailed clinical pharmacology information regarding Ga 68 gozetotide, refer to Section 6 of the multi-disciplinary review of the RLD application, NDA 212643, dated November

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23, 2020. The clinical pharmacology content for the ILLUCCIX package insert will be transferred from the RLD package insert.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Although the pharmacokinetics, dosimetry, and distribution study was not adequately powered to conclude comparability, results obtained with Ga 68 gozetotide prepared by the Applicant's kit and the RLD method were similar. In conjunction with the biopharmaceutics assessment, in vitro data, and additional clinical evaluations mentioned above, this study supports reliance on the RLD for safety and effectiveness.

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

The recommended dosing is identical to that of the RLD and is appropriate for the same indicated patient populations with prostate cancer as the RLD.

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

No. An alternate dosing regimen is not required for subpopulations based on intrinsic patient factors.

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

Yes. Drug interaction recommendations will be transferred from the RLD prescribing information as follows:

<u>Section 2.2: Recommended Dosage and Administration Instructions</u>

Unless contraindicated, 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.

<u>Section 7: Drug Interactions</u>

Androgen deprivation therapy and other therapies targeting the androgen pathway, such as androgen receptor antagonists, 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.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7. Listing of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Phase 3 trials to support efficacy and safety							
BCR-RET-01	N/A	Retrospective, central read, open-label	Single 100 to 300 MBq i.v. dose of Ga 68 gozetotide	Patient-level correct detection rate and region-level verified localization rate for recurrent prostate cancer by composite reference standard	422	Patients with biochemically recurrent prostate cancer	1 site in U.S.
Other trials pertinent to the review of efficacy							
ANMI-PG01-C301	N/A	Retrospective, observational	Single 185 MBq ±10% i.v. dose of Ga 68 gozetotide	Patient-level and region-level sensitivity and patient-level specificity for recurrent prostate cancer by composite reference standard	200	Patients with recurrent prostate cancer after treatment with prostatectomy or radiotherapy	1 site in Italy
Other trials pertinent to the review of safety							
PSMA-617-01	NCT03511664	Prospective, open-label, randomized	Single 111 to 185 MBq i.v. dose of Ga 68 gozetotide	Adverse events	206	Patients with progressive metastatic castrate resistant prostate cancer	95 principal investigators (51 in U.S.), 9 countries (U.S., Belgium, Canada, Denmark, France, Germany, Netherlands, Sweden, United Kingdom)

Source: FDA clinical reviewer.
Abbreviations: BCR = biochemical recurrence, i.v. = intravenous, N/A = Not Applicable, no. = number, PSMA = prostate-specific membrane antigen, U.S.= United States of America
Note: The results from PSMA-617-01 in this application are from a temporal subset of the full trial and may not include all trial sites.

7.2. Review Strategy

The Applicant has proposed to rely on FDA's findings of effectiveness and safety for the RLD, Ga 68 gozetotide injection under NDA 212643, as the primary support for this application. As discussed in Section 6, an issue for bridging between the Applicant's kit and the RLD relates to the different maximum mass doses of these products.

While the mass dose of radioactive Ga 68 gozetotide to be administered is minimal, ranging from 1.1 to 2.6 ng for a 3 to 7 mCi dose, the mass dose of non-radioactive gozetotide is substantially higher. The amount of gozetotide present in a single patient batch of the RLD is 5 µg, and it would be extremely unlikely for a patient to receive a dose of more than 10 µg gozetotide through potential pooling of batches. For the Applicant's kit, the amount of gozetotide used in a multidose production batch is 25 µg, and administered mass dose could range from approximately 1.5 µg to 25 µg per patient dose. Of note, the maximum mass dose of 25 µg gozetotide was frequently administered to patients in clinical trials. Because non-radioactive gozetotide can still bind to PSMA and is expected to compete for binding sites with Ga 68 gozetotide, the difference in total mass dose between the kit product and injection product could have an impact on imaging effectiveness.

To address this issue, the Applicant supplied mass dose data from the BCR-RET-01 study. As discussed further in Section 8.1 of this review, this study administered Ga 68 gozetotide prepared using the Applicant's kit and a method used at the study site, Memorial Sloan Kettering Cancer Center (MSKCC). The MSKCC method of preparation was distinct from both the Applicant's kit and the RL (b) (4)

Total mass dose administered in the BCR-RET-01 study was stratified by PET positivity to investigate the possibility that increasing amounts of non-radioactive gozetotide would compete for Ga 68 gozetotide binding and decrease the lesion detection rate. Data from both the Applicant's kit and the MSKCC method were analyzed in this general evaluation of the impact of gozetotide mass dose on lesion detection. Of note, these analyses were not validated against a reference standard because of study design issues further described in Section 8 of this review.

The amount of gozetotide administered in each patient dose in BCR-RET-01 ranged from 2.7 µg to 25 µg for Ga 68 gozetotide produced by the Applicant's kit and 3 µg to 11 µg for drug produced by the MSKCC method. There were 28 patients in the study (7%) who received a mass dose of 5 µg or less. The distribution of mass doses stratified by production method and by overall PET result is shown in Table 8.

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Table 8. Administered Gozetotide Mass Dose Distribution in BCR-RET-01, Stratified by Drug Preparation Method and by PET Reading Result

		Patients	Mass Dose (µg)			
Preparation	Patients Dosed	With Mass Dose Data	Mean ± SD	25th Percentile	Median	75th Percentile
Applicant's kit	309	279	13.9 ± 4.7	10.3	12.7	16.7
PET positive	193	171	14.0 ± 4.8	10.7	12.7	16.7
PET negative	86	78	13.8 ± 4.7	10.0	13.3	15.7
MSKCC	129	129	7.4 ± 2.0	6.0	8.0	9.0
PET positive	102	102	7.4 ± 2.0	6.0	8.0	8.8
PET negative	27	27	7.3 ± 2.3	4.6	8.2	9.4
Total	438	408	11.8 ± 5.1	8.6	10.7	13.7
PET positive	317	295	11.7 ± 5.1	8.4	10.3	13.3
PET negative	121	113	12.2 ± 5.1	9.4	11.3	14.7

Source: FDA clinical reviewer
Abbreviations: MSKCC = Memorial Sloan Kettering Cancer Center, PET = positron emission tomography, SD = standard deviation
Note: PET result is from Reader 1.

As expected, based on gozetotide mass dose used for each production batch, the administered mass dose was higher in patients receiving drug produced with the Applicant's kit. There was, however, little difference in the distribution of mass dose between PET positive and PET negative patients for either method. Additional exploratory analyses using baseline PSA level as a surrogate for tumor burden and the number of PET positive subregions as a potentially more sensitive measure of imaging performance also did not show evidence of an effect of varying mass dose over the range in this study. Thus, the differences in mass dose between the Applicant's kit and the RLD are not expected to impact imaging performance.

As discussed in Section 6 of this review, the above clinical mass dose evaluation contributed to the establishment of a bridge between the Applicant's kit and the RLD. Since FDA's previous findings of effectiveness and safety for the RLD can be relied upon for approval of the Applicant's kit, additional efficacy data from the BCR-RET-01 study is only briefly reviewed in Section 8.1. Study ANMI-PG01-C301 will not be further discussed in this review as it was intended to provide only secondary support of efficacy and because of limitations in study design. The Applicant's clinical safety data with Ga 68 gozetotide are reviewed in Section 8.2 for the purpose of excluding any new safety signals that were not identified at the time of approval of the RLD.

Analyses performed by the clinical reviewer used SAS Enterprise Guide version 8.1. Two-sided 95% confidence intervals for proportions used the method of Clopper-Pearson.

Reference ID: 4905337

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BCR-RET-01

Trial Design

BCR-RET-01 was an open-label study of Ga 68 gozetotide PET for imaging of PSMA-expressing prostate adenocarcinoma. The study entailed retrospective central reading of images from patients enrolled from August 4, 2017, to August 31, 2019, in a prospective expanded access protocol at one site in the United States, MSKCC. The expanded access protocol enrolled adult men with biopsy-proven prostate adenocarcinoma who had been treated with definitive local therapy. All patients had biochemical recurrence of prostate cancer defined as serum PSA level of 0.2 ng/mL or higher in at least two consecutive tests within 6 months of consent. BCR-RET-01 enrolled the subset of these patients who had PSA level of ≥0.2 ng/mL measured at least 6 weeks after radical prostatectomy with confirmatory persistent PSA of >0.2 ng/mL or who had a rise in PSA of at least 2 ng/mL above nadir for patients who had radiation therapy without radical prostatectomy. These PSA cutoffs were based on American Urological Association (Cookson et al., 2007) and American Society for Radiation Oncology-Phoenix (Roach et al., 2006) definitions of biochemical recurrence.

After enrollment, each patient was to receive 100 to 300 MBq (2.7 to 8.1 mCi) Ga 68 gozetotide intravenously, with a target dose of 2.5 MBq/kg. Dose selection was supported by reports of successful imaging at similar doses that were published prior to study initiation. Ga 68 gozetotide was produced by either the Applicant's kit or by a different method specific to MSKCC. The study was not designed to compare Ga 68 gozetotide produced by the different methods and the procedure for allocation of patients to drug production method was not specified in the protocol. Administration of 20 mg furosemide intravenously 10 to 20 minutes after Ga 68 gozetotide, along with oral hydration, was optional. This measure was intended to reduce the potential of interference from radioactivity in the urinary tract on imaging. Approximately 60 to 90 minutes after injection, patients were scanned using PET/CT.

PET/CT images were transferred to a contract research organization, (b) (4) (b) (4) for centralized interpretation. The images were evaluated by three blinded, independent, board-certified nuclear medicine physicians. Training was required for the readers prior to participation in the study. Each reader recorded whether 53 subregions grouped into 4 regions (prostate bed, pelvic lymph nodes, skeleton, and other distant sites) were PET positive. An additional 'other' subregion was also evaluated, and if positive the specific location was recorded. For prostate bed, skeleton, and other distant site lesions, positive was defined as containing uptake that was focal and greater than physiologic background activity. Pelvic lymph node lesions were considered positive if uptake was focal and greater than blood pool.

Redacted histopathology and conventional imaging reports found in the MSKCC medical record dated within 6 months before or after the Ga 68 gozetotide PET served as source data for the composite reference standard. These reports were transferred to (b) (4) (b) (4) and evaluated in the same subregions as the investigational images by a fourth independent, board-certified nuclear medicine physician. The reference standard reader was blinded to the investigational PET images and the results from the blinded PET readers results from a patient's report were used to classify each of the patient's subregions as positive for prostate cancer, negative for prostate cancer, or not available for subregions with no related information. For conventional imaging reports, no associated images were available to the reference standard reader. The overall composite reference result for each subregion was defined as positive if any report was read as positive in that subregion, negative if any report was read as negative and no report was read as positive in that subregion, and otherwise as not available.

Comparison of the PET reads to the reference standard required matching location at the subregion level. For the 'other' subregion, an independent medic determined whether the recorded locations matched. Regions were considered true positive (TP) if they contained a true positive subregion, and patients were considered true positive if they had a true positive region. Patients and regions that were PET positive but not true positive were termed 'non-TP', regardless of whether the corresponding subregion was called negative or not available for the reference standard.

A summary of the data collected and information sources is provided in Table 9, in which the original MSKCC expanded access protocol is referred to as the "prospective study", retrospective medical record review is referred to as "medical chart", and prospective review of Ga 68 gozetotide PET scans and reference standard reports is referred to as "re-read".

Table 9. BCR-RET-01 Data Sources

Data	Prospective Study	Medical Chart	Re-Read
Informed consent	X		
Scan ID	X		
Eligibility for participation	X		
Demographics	X	X	
Ga-68 gozetotide scan	X		X
Conventional imaging reports	X	X	X
Histopathology/biopsy reports	X	X	X
Vital signs/Laboratory results		X	
Electrocardiograms		X	
Pathology/Cancer therapies	X	X	
Record medical events/AEs	X	X	
Other follow-up		X	X
Efficacy assessments (TP, FP)			X

Source: Adapted from Table 2 of BCR-RET-01 clinical study report
Abbreviations: AEs = adverse events; FP = false positive; ID = identification; TP = true positive

Study Endpoints

The co-primary endpoints were patient-level correct detection rate (CDR) and region-level verified localization rate (VLR). Per the protocol, "Patient-level CDR is defined as the percentage of patients who have at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any coexistent false positive findings, out of all patients who are scanned" and "region-level VLR is defined as the percentage of regions containing at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent false positive findings within the same region, out of all regions containing at least one PET-positive finding".

Statistical Analysis Plan

The statistical analysis plan defines six efficacy analysis populations, with different populations for each of the co-primary endpoints. All populations were based on patients who participated in the MSKCC expanded access study, met the additional PSA level inclusion criterion for BCR-RET-01, and received a Ga 68 gozetotide PET scan. The populations used for the primary analyses were:

- CDR: Full Patient Analysis Set: all patients who had a Ga 68 gozetotide PET/CT scan
- VLR: Full Region Analysis Set: all regions with at least one Ga 68 gozetotide PET/CT positive finding

The threshold for the CDR co-primary endpoint in the Full Patient Analysis Set was set at 20%, against which the lower bound of the 95% confidence interval was compared for each reader. For the region-level VLR co-primary endpoint, the Applicant first determined the VLR for each patient, then calculated the mean VLR among all patients. The lower bound of the 95% confidence interval of this mean VLR was compared to a threshold of 10%.

During analysis, it was discovered that some patients did not have sufficient data to determine a reference standard result. The Applicant therefore changed the primary efficacy analysis populations to:

- CDR: Patient Efficacy Evaluable Set: all patients who had a Ga 68 gozetotide PET/CT scan and at least one form of reference standard
- VLR: Region Efficacy Evaluable Set: all regions with at least one Ga 68 gozetotide PET/CT positive finding in patients who had at least one form of reference standard

Protocol Amendments

No protocol amendments were reported by the Applicant.

Reference ID: 4905337

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant states that both the expanded access MSKCC study and BCR-RET-01 were performed in compliance with good clinical practice and with IRB oversight.

Financial Disclosure

No relevant financial disclosures were made by the Applicant or by the central readers.

Patient Disposition

A total of 438 patients were enrolled in the MSKCC expanded access study and met the BCR-RET-01 enrollment criteria during the study period. Of these, 16 patients were excluded from the Full Patient Analysis Set because it was unclear at the time of analysis whether they had received Ga 68 gozetotide. Thus, the Full Patient Analysis Set contained 422 patients. Approximately 70% of patients (295 of 422) in the Full Patient Analysis Set received Ga 68 gozetotide produced by the Applicant's kit.

Protocol Violations/Deviations

In the Full Patient Analysis Set, 51 of 422 patients (12%) had a protocol deviation recorded. The most common protocol deviation was screening prior to consent, occurring in 35 patients. Fifteen patients had conventional imaging more than 180 days before or after the Ga 68 gozetotide PET scan. One patient had an adverse event reported outside the protocol-defined 24 hour window.

Table of Demographic Characteristics

Demographic features of patients enrolled in BCR-RET-01 are shown in Table 10. The age distribution is reasonable for patients with biochemically recurrent prostate cancer. Most patients were white and not Hispanic or Latino. The patients who received Ga 68 gozetotide prepared using the Applicant's kit had similar demographics to the overall study sample.

Table 10. Demographics of Patients in BCR-RET-01

Parameter	Full Patient Analysis Set (n=422) n (%)	Applicant's Kit (n=295) n (%)
Age		
Mean years (SD)	68.4 (8.6)	68.7 (8.4)
Median (years)	69.0	69.4
Min, max (years)	44, 91	44, 91
Age Group		
≤ 65 years	132 (31%)	87 (29%)
> 65 years	290 (69%)	208 (71%)

Parameter	Full Patient Analysis Set (n=422) n (%)	Applicant's Kit (n=295) n (%)
Race		
White	362 (86%)	248 (84%)
Black or African American	19 (5%)	19 (6%)
Asian	9 (2%)	8 (3%)
Missing	32 (7%)	20 (7%)
Ethnicity		
Hispanic or Latino	15 (4%)	13 (4%)
Not Hispanic or Latino	389 (92%)	268 (91%)
Missing	18 (4%)	14 (5%)

Source: BCR-RET-01 clinical study report Table 7 and FDA clinical reviewer (Applicant's Kit).
Abbreviations: max = maximum, min = minimum, n = number of patients, SD = standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Selected baseline characteristics of the men enrolled in BCR-RET-01 relevant to prostate cancer are shown in Table 11. Most patients had received a radical prostatectomy at some point in their treatment course. The median PSA was 1.1 ng/mL, which is reasonable for a study of this design where PET drug performance should be tested in patients who have a wide range of PSA levels. Roughly one-third of patients had PSA levels at enrollment of less than 0.5 ng/mL. These patients would be expected to have lower disease volume with more difficult to localize lesions. There was a slight trend to lower PSA levels in the group of patients who received Ga 68 gozetotide prepared using the Applicant's kit compared to the Full Patient Analysis Set. Note that the differences in PSA level were more substantial when comparing patients dosed with product made with the Applicant's kit directly to those who received Ga 68 gozetotide made by the MSKCC method. However, because this does not significantly impact regulatory evaluation of BCR-RET-01 and because the study was not designed to compare the two preparation methods, results are not separately shown for patients who received the MSKCC product.

Table 11. Selected Baseline Characteristics for Patients in BCR-RET-01

Parameter	Full Patient Analysis Set (n=422) n (%)	Applicant's Kit (n=295) n (%)
PSA		
Mean, ng/mL (SD)	10.50 (84.09)	6.47 (43.59)
Median, ng/mL	1.10	0.93
Min, max, ng/mL	0.15, 1550.63	0.18, 706.66
PSA Group		
< 0.5 ng/mL	132 (31%)	98 (33%)
0.5-2 ng/mL	125 (30%)	100 (34%)
> 2 ng/mL	165 (39%)	97% (33%)
Radical Prostatectomy		
Yes	343 (81%)	236 (80%)
No	78 (18%)	58 (20%)
Missing	1 (<1%)	1 (<1%)

Source: BCR-RET-01 clinical study report Table 7 and FDA clinical reviewer (Applicant's Kit).
Abbreviations: max = maximum, min = minimum, n = number of patients, PSA = prostate-specific antigen, SD = standard deviation

Efficacy Results and Additional Analyses

This review will focus on the patient-level correct detection rate co-primary endpoint in the Full Patient Analysis Set as initially proposed in the protocol, supplemented by exploratory patient-level and region-level positive predictive value analyses, to illustrate issues of study design and execution that ultimately led to the conclusion that BCR-RET-01 was not an adequate and well-controlled efficacy study for regulatory purposes. Similar arguments would apply to the region-level VLR co-primary endpoint.

As shown in Table 12, the correct detection rate, or true positive detection rate, ranged from 29% to 33% for all patients in the Full Patient Analysis Set at the lower bound of the 95% confidence interval. This result exceeded the Applicant's predefined threshold of 20% for all readers. It is also apparent that a substantial portion of patients with positive results on the Ga 68 gozetotide PET, ranging from 23% to 26%, could not be categorized as true positive or false positive due to lack of reference standard information in a PET positive subregion. As at least some of these patients would likely be true positive, the measured CDR values represent minimum estimates.

An additional metric should be considered with CDR to place the false positive rate in context. Specificity is difficult to define in the biochemically recurrent prostate cancer setting due to the assumed low true negative rate. Thus, patient-level positive predictive value was explored. The measured patient-level positive predictive value (PPV) was 52% to 62%, however this does not include the patients who lacked reference standard information in a PET positive subregion. Such a situation raises the possibility of inaccurate PPV estimation if there was biased patient selection for reference standard determination. There are many factors that could predispose to bias, for example the difficulty in obtaining reference standard information for smaller lesions, which may also be more likely to be false positive when found on PET.

Table 12. Patient-Level Performance of Ga 68 Gozetotide for Localization of Biochemically Recurrent Prostate Cancer in the Full Patient Analysis Set

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	FPAS (n=422)	Applicant Kit (n=295)	FPAS (n=422)	Applicant Kit (n=295)	FPAS (n=422)	Applicant Kit (n=295)
True positive	159	104	155	103	143	94
False positive	75	46	110	70	75	43
PET positive without reference standard	71	53	94	72	78	58
PET negative	117	92	63	50	126	100
Fraction PET positive	0.72	0.69	0.85	0.83	0.70	0.66
CDR, point estimate	0.38	0.35	0.37	0.35	0.34	0.32
(95% CI)	(0.33, 0.42)	(0.30, 0.41)	(0.32, 0.42)	(0.29, 0.41)	(0.29, 0.39)	(0.27, 0.38)
PPV, point estimate	0.68	0.69	0.58	0.60	0.66	0.69
(95% CI)	(0.62, 0.74)	(0.61, 0.77)	(0.52, 0.64)	(0.52, 0.67)	(0.59, 0.72)	(0.60, 0.76)

Source: BCR-RET-01 clinical study report (Tables 11 and 12) and FDA clinical reviewer
Abbreviations: CDR = correct detection rate (true positive/number of patients scanned in group), CI = confidence interval, FPAS = full patient analysis set, n = number of patients, PET = positron emission tomography, PPV = positive predictive value (true positive/(true positive + false positive))

Reference standard determinations were made on the basis of available clinical histopathology and radiology reports. For radiology reports, lesion matching between the Ga 68 gozetotide PET and the reference standard was limited to the subregion-level because the reader did not have access to the source images. As the images were not necessarily obtained for evaluating prostate cancer disease status, the protocols and image evaluations were not optimized for this purpose. Difficulties also arose when translating clinical interpretations that contained qualifiers such as 'suspected' into a binary result. The most commonly used types of reference standard information are shown in Table 13. These include imaging modalities that have low sensitivity and low specificity for prostate cancer, such as dual-energy x-ray absorptiometry. Together, these issues very likely lowered the number of true positive and raised the number of false positive determinations. However, the numerical effect on the endpoint results cannot be precisely determined.

Table 13. Number of Patients With Reference Standard Information Available in the Full Patient Analysis Set

	Performed Before Ga 68 Gozetotide PET		Performed After Ga 68 Gozetotide PET	
Modality	FPAS (n=422) n (%)	Applicant's Kit (n=295) n (%)	FPAS (n=422) n (%)	Applicant's Kit (n=295) n (%)
Histopathology	0	0	57 (14%)	38 (13%)
CT	120 (28%)	74 (25%)	96 (23%)	62 (21%)
MRI	179 (42%)	116 (39%)	123 (29%)	97 (33%)
Bone scan	103 (24%)	65 (22%)	36 (9%)	24 (8%)
^{18}F fluciclovine PET	18 (4%)	15 (5%)	3 (<1%)	0
^{18}F FDG PET	42 (10%)	11 (4%)	26 (6%)	9 (3%)
X-ray	23 (5%)	14 (5%)	32 (8%)	19 (6%)
Ultrasound	11 (3%)	9 (3%)	17 (4%)	13 (4%)
DEXA	11 (3%)	7 (2%)	53 (13%)	39 (13%)
Any reference standard data	267 (63%)	173 (59%)	249 (59%)	168 (57%)

Source: FDA clinical reviewer
Abbreviations: CT = computed tomography, DEXA = dual-energy X-ray absorptiometry, FDG = fluorodeoxyglucose, FPAS = full patient analysis set, MRI = magnetic resonance imaging, n = number of patients, PET = positron emission tomography
Note: A patient could have multiple sources of reference standard data obtained both before and after the investigational PET and therefore may be counted multiple times. Modalities used in less than 10 patients are not separately listed in the table but are included for the "Any reference standard data" row.

Reference standard information other than histopathology was collected from both before and after the Ga 68 gozetotide PET was performed. An exploratory subgroup analysis was performed to evaluate whether information available at baseline could have affected the study results (Table 14).

Table 14. Patient-Level Performance of the Applicant's Kit for Localization of Biochemically Recurrent Prostate Cancer in the Full Patient Analysis Set, Stratified by Presence and Result of Conventional Imaging Performed Prior to the Investigational PET

	Reader 1		Reader 2		Reader 3	
Diagnostic Performance Measure	**Baseline + (n=99)**	**Baseline – or Absent (n=196)**	**Baseline + (n=99)**	**Baseline – or Absent (n=196)**	**Baseline + (n=99)**	**Baseline – or Absent (n=196)**
True positive	66	38	64	39	60	34
False positive	16	30	18	52	10	33
PET positive without reference standard	1	52	2	70	4	54
PET negative	16	76	15	35	25	75
Fraction PET positive	0.84	0.61	0.85	0.82	0.75	0.62
CDR, point estimate	0.67	0.26	0.66	0.31	0.63	0.24
(95% CI)	(0.57, 0.76)	(0.19, 0.34)	(0.56, 0.75)	(0.23,0.40)	(0.53, 0.73)	(0.17, 0.32)
PPV, point estimate	0.80	0.56	0.78	0.41	0.86	0.51
(95% CI)	(0.70, 0.88)	(0.43, 0.68)	(0.68, 0.86)	(0.33, 0.54)	(0.75, 0.93)	(0.38, 0.63)

Source: FDA clinical reviewer
Abbreviations: + = positive, - = negative, CDR = correct detection rate (true positive/number of patients scanned in group), CI = confidence interval, n = number of patients, PET = positron emission tomography, PPV = positive predictive value (true positive/(true positive + false positive))

For all readers, the patient-level CDR and PPV were higher among the patients who had a positive result on at least one imaging test performed before the Ga 68 gozetotide PET. While the difference in CDR may be driven by having fewer patients without informative reference standard data in the baseline positive group, this is not the case for PPV, which was determined only in patients with informative reference standard data. The decline in PPV for patients without positive baseline imaging raises concern that the study may not be adequate to support a non-adjunctive imaging indication. Based on data reviewed for prior approvals of other formulations of Ga 68 gozetotide and for the related drug piflufolastat F 18, it is more likely that the apparently low performance in patients with negative or absent reference standard information at baseline is due to study design rather than a drug-related issue.

Because the majority of patients with biochemically recurrent prostate cancer are assumed to have recurrent disease, and the anticipated clinical use of Ga 68 gozetotide PET is to localize this disease, it is of interest to measure test performance at a more granular level than the patient-level. Table 15 summarizes the regional distribution of PET findings and the region-level PPV in BCR-RET-01.

Table 15. Region-Level Performance of the Applicant's Kit for Localization of Biochemically Recurrent Prostate Cancer in the Full Region Analysis Set

	Reader 1		Reader 2		Reader 3	
Region	PET + Regions Evaluated/ Total	PPV Point Estimate (95% CI)	PET + Regions Evaluated/ Total	PPV Point Estimate (95% CI)	PET + Regions Evaluated/ Total	PPV Point Estimate (95% CI)
Prostate/prostate bed	80/102	0.46 (0.35, 0.58)	74/113	0.42 (0.31, 0.54)	30/45	0.67 (0.47, 0.83)
Pelvic lymph node	59/83	0.41 (0.28, 0.54)	62/89	0.34 (0.22, 0.47)	54/80	0.48 (0.34, 0.62)
Bone	47/62	0.74 (0.60, 0.86)	57/83	0.63 (0.49, 0.76)	51/63	0.67 (0.52, 0.79)
Other distant sites	43/66	0.63 (0.47, 0.77)	83/138	0.41 (0.30, 0.52)	55/94	0.62 (0.48, 0.75)
Total	229/313	0.54 (0.47, 0.60)	276/423	0.44 (0.38, 0.50)	190/282	0.60 (0.53, 0.67)

Source: FDA clinical reviewer
Abbreviations: + = positive, CI = confidence interval, n = number of regions, PET = positron emission tomography, PPV = positive predictive value
Note: No adjustment is made for within-patient correlations in this exploratory analysis.

For all readers, the PPV was highest in the bone region and lowest in the pelvic lymph node region, though the differences between regions could be small depending on the reader. At the region-level, the fraction of PET positive regions that were missing reference standard data (27% to 35%) was generally greater than at patient-level, indicating that even in patients who could be categorized as true positive or false positive, not all PET positive regions were characterized.

Dose/Dose Response

The intended radioactivity dose range of Ga 68 gozetotide was 2.7 to 8.1 mCi. The administered dose in the Full Patient Analysis Set was 6.6 mCi ± 1.2 mCi (mean ± standard deviation). Two patients received doses outside the prescribed range, 2.2 mCi and 2.6 mCi. In the subgroup of patients who were given the drug produced using the Applicant's kit, the administered dose was 6.5 mCi ± 1.2 mCi (mean ± standard deviation). As noted previously, the administered mass dose of gozetotide ranged from 2.7 µg to 25 µg per patient with a mean of 11.8 µg (see Table 8).

8.1.3. Integrated Assessment of Effectiveness

BCR-RET-01 was not considered an adequate and well-controlled study of effectiveness for regulatory purposes, primarily due to issues with the quality of the reference standard information, as discussed in Section 8.1.2 of this review. However, the Applicant proposes to rely on FDA's findings of effectiveness for Ga 68 gozetotide injection in NDA 212643. Given the adequate bridge to this RLD, as described in Section 6 of this review, approval for the indications listed in the prescribing information for the RLD is supported. Namely, approval of Ga 68 gozetotide prepared by the Applicant's kit is supported for imaging of prostate cancer in

two populations: 1) men with suspected metastasis who are candidates for initial definitive therapy, and 2) men with suspected recurrence based on elevated serum PSA.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data in this application were drawn from three studies, BCR-RET-01, PSMA-617-01, and ANMI-PG01-C301. In addition, the Applicant is relying on FDA's findings of safety for the RLD, Ga 68 gozetotide injection under NDA 212643. Refer to Section 8.2 of the previous multi-disciplinary review of NDA 212643 dated November 23, 2020, for safety results from that application.

Because ANMI-PG01-C301 was based on retrospective chart review without predefined safety data collection and no treatment-emergent adverse events were reported, this study will not be discussed further. Safety data from studies BCR-RET-01 and PSMA-617-01 are discussed further in this section of the current review.

No specific safety issues were encountered during the Applicant's development of the drug.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 628 patients were evaluated for safety in the BCR-RET-01 and PSMA-617-01 studies. For BCR-RET-01, all patients who were known to have received Ga 68 gozetotide at the time of analysis were included in the safety set. Therefore, the 16 patients described in Section 8.1.2 who had uncertain administration of the investigational drug at the start of analysis were excluded. PSMA-617-01 was derived from the Endocyte VISION trial of Lu 177 PSMA-617 performed under IND 133661 which used Ga 68 gozetotide PET results for enrollment purposes. All patients administered Ga 68 gozetotide from November 26, 2018, to June 6, 2019, were included in the PSMA-617-01 safety set, representing a subset of the larger VISION trial, which was ongoing at the time of submission of this application.

Briefly, VISION was a multi-center, multi-national trial that enrolled patients with progressive, PSMA-positive metastatic castrate resistant prostate cancer who had previously been treated with a taxane. During screening, patients received a PET scan using 3 to 5 mCi of Ga 68 gozetotide produced using the Applicant's kit. Furosemide was co-administered at the discretion of the study site.

Patients who have progressive metastatic castrate resistant prostate cancer typically have greater extent of disease than patients categorized as biochemically recurrent. In addition, the patients in the VISION study were exposed to multiple lines of therapy and may have had additional comorbidities. Results of BCR-RET-01 and PSMA-617-01 were not pooled in this

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review due to these differences in patient population and (as shown in Table 16) dose of Ga 68 gozetotide.

Table 16 summarizes the baseline characteristics of patients in the BCR-RET-01 and PSMA-617-01 studies. The safety population was predominantly white. However, we are not aware of data to suggest that race will influence likelihood or severity of adverse events (AEs).

Table 16. Baseline Characteristics of Patients in the BCR-RET-01 and PSMA-617-01 Studies

Parameters	BCR-RET-01 (n=422) n (%)	PSMA-617-01 (n=206) n (%)
Age		
Mean years (SD)	68.4 (8.6)	70.7 (7.8)
Median (years)	69.0	71.5
Min, max (years)	44, 91	47, 94
Age Group		
≤ 65 years	132 (31%)	54 (26%)
> 65 years	290 (69%)	152 (74%)
Race		
White	362 (86%)	186 (90%)
Black or African American	19 (5%)	4 (2%)
Asian	9 (2%)	1 (<1%)
American Indian or Alaskan Native	0	2 (1%)
Missing	32 (7%)	13 (6%)
Ethnicity		
Hispanic or Latino	15 (4%)	1 (<1%)
Not Hispanic or Latino	389 (92%)	153 (74%)
Missing	18 (4%)	52 (25%)
Dose		
Dose (mCi) (SD)	6.6 (1.2)	4.4 (0.7)

Source: BCR-RET-01 clinical study report (Table 7) and PSMA-617-01 clinical study report (Tables 1, 2, and 8)
Abbreviations: max = maximum, min = minimum, n = number of patients, SD = standard deviation

Adequacy of the safety database:

The size and demographic distribution of the safety database is acceptable.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

In BCR-RET-01, patients were monitored for adverse events from the start of Ga 68 gozetotide administration through 120 minutes post-injection. Any adverse event reported up to 1 day post-injection could be included in the safety data, though no routine monitoring for adverse events was performed after the 120 minute time point. Adverse event severity was graded using Common Terminology Criteria for Adverse Event version 4.0 and investigator-assessed relatedness was required for capture of adverse events. Adverse events were coded for analysis using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

In PSMA-617-01, adverse events were reported from time of consent through the earlier of 6 days post-injection of Ga 68 gozetotide or administration of the other investigational drug, Lu 177 PSMA-617. Adverse event data were collected regardless of whether the patient continued to the treatment portion of the study. Severity was graded using Common Terminology Criteria for Adverse Event version 5.0 and relatedness was assessed as definitely not related, probably not related, possibly related, probably related, or definitely related. Adverse events were coded for analysis using MedDRA version 21.0.

The coding of verbatim terms to MedDRA lowest level terms was audited as a component of this review and no substantial issues were found.

Routine Clinical Tests

No vital sign, safety laboratory, or electrocardiogram (ECG) data collection was planned in the MSKCC expanded access protocol that BCR-RET-01 was based on. However, the Applicant received and analyzed any results that were available from standard of care assessments within 1 week before or after the Ga 68 gozetotide PET scan.

In PSMA-617-01, vital signs, safety labs, and ECG data are available at baseline prior to Ga 68 gozetotide administration, however post-administration results are not. Thus, these data are noninformative with respect to the safety of Ga 68 gozetotide and will not be discussed further in this review.

8.2.4. Safety Results

Deaths

Two patient deaths were reported in PSMA-617-01.

Patient (b) (6) was a 71 year-old man who had metastatic castrate resistant prostate cancer, dorsal pain, and asthenia. Whether he received Lu 177 PSMA-617 was not stated. At 34 days following administration of Ga 68 gozetotide he was admitted to the hospital for anemia with hemoglobin of 6.9 g/dL. After treatment with transfusion and a 4 day hospital stay, the event was considered resolved. However, 46 days after administration of Ga 68 gozetotide he presented with sudden onset of central nervous system “aggravation”. Head imaging showed brain hematomas, thought to be due to bleeding meningeal metastases. On day 47, the patient died. The investigator and Sponsor both assessed the events of anemia and brain hematomas as unrelated to Ga 68 gozetotide. Due to the amount of time that passed between the administration of Ga 68 gozetotide and the events as well as the presence of a more likely explanation for the events (metastatic prostate cancer), this assessment is reasonable.

Patient (b) (6) was a 69 year-old man with a history of metastatic castrate resistant prostate cancer, right lower extremity edema, abdominal distention, and perennial rhinitis. Whether he received Lu 177 PSMA-617 was not stated. At 10 days following administration of

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Ga 68 gozetotide, he was admitted to the hospital for pneumonia and treated with antibiotics. During this admission, he was also diagnosed with dermatomyositis. At 22 days following administration of Ga 68 gozetotide, the patient was admitted to the hospital due to dermatomyositis and on day 51 he died. The investigator assigned the cause of death as dermatomyositis. The investigator and Sponsor assessed the events of pneumonia and dermatomyositis as unrelated to Ga 68 gozetotide. Because the presence of metastatic prostate cancer can predispose to dermatomyositis and may also increase risk of infection through immunosuppression, this assessment is reasonable.

No patient death was reported in BCR-RET-01.

Serious Adverse Events

As shown in Table 17, a total of 21 treatment-emergent serious adverse events (SAEs) were reported in PSMA-617-01, distributed among 11 patients. Four of these events in two patients are discussed in the prior section as they resulted in patient death. The Applicant assessed all SAEs as unrelated to Ga 68 gozetotide. It is noted that most of the reported SAEs are either relatively common in older adults (i.e., gastritis, chest pain) or associated with metastatic prostate cancer and its treatment (i.e., anemia, bone pain, constipation).

Table 17. Listing of Treatment-Emergent Serious Adverse Events in PSMA-617-01

MedDRA SOC or PT	PSMA-617-01 (n=206) n (%)
Blood and lymphatic system disorders	3 (1.5%)
Bicytopenia	2 (1.0%)
Anemia	1 (0.5%)
Gastrointestinal disorders	2 (1.0%)
Constipation	2 (1.0%)
Gastritis	1 (0.5%)
General disorders and administration site conditions	2 (1.0%)
Chest pain	1 (0.5%)
General physical health deterioration	1 (0.5%)
Infections and infestations	2 (1.0%)
Pneumonia	1 (0.5%)
Urinary tract infection pseudomonal	1 (0.5%)
Nervous system disorders	2 (1.0%)
Cerebral hematoma	1 (0.5%)
Spinal cord compression	1 (0.5%)
Injury, poisoning, and procedural complications	1 (0.5%)
Fibula fracture	1 (0.5%)
Radius fracture	1 (0.5%)
Tibia fracture	1 (0.5%)
Ulna fracture	1 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.5%)
Bone pain	1 (0.5%)
Neoplasms benign, malignant, and unspecified	1 (0.5%)
Tumor associated fever	1 (0.5%)

MedDRA SOC or PT	PSMA-617-01 (n=206) n (%)
Renal and urinary disorders	1 (0.5%)
Acute kidney injury	1 (0.5%)
Hematuria	1 (0.5%)
Skin and subcutaneous tissue disorders	1 (0.5%)
Dermatomyositis	1 (0.5%)

Source: PSMA-617-01 clinical study report, Table 9.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients, PT = preferred term, SOC = system organ class
Note: The numbers in this table refer to patients rather than events.

No SAEs were reported in BCR-RET-01.

Dropouts and/or Discontinuations Due to Adverse Effects

No study dropouts or discontinuations due to adverse effects were reported in BCR-RET-01 or PSMA-617-01.

Significant Adverse Events

Other than the previously listed reports of deaths and SAEs, no significant AEs were reported.

Treatment-Emergent Adverse Events and Adverse Reactions

A total of 109 treatment-emergent AEs were reported in 48 of 206 patients (23%) in PSMA-617-01. Events that occurred in more than one patient are listed in Table 18. The most commonly reported adverse events were asthenia, arthralgia, constipation, and anemia. The greatest adverse event severity was grade 1 in 16 of 48 patients (33%), grade 2 in 20 patients (42%), grade 3 in 10 patients (21%), and grade 5 in 2 patients. Severity was not assessed for three AEs, bone pain, dyspnea, and lung disorder. The grade 3 events that were not considered SAEs were arthralgia, asthenia, and metastases to meninges.

Table 18. Listing of Treatment-Emergent Adverse Events Occurring in More Than One Patient in PSMA-617-01

MedDRA SOC or PT	PSMA-617-01 (n=206) n (%)
Musculoskeletal and connective tissue disorders	
Arthralgia	5 (2.4%)
Bone pain	3 (1.5%)
Musculoskeletal chest pain	2 (1.0%)
General disorders and administration site conditions	
Asthenia	6 (2.9%)
Fatigue	2 (1.0%)
Gastrointestinal disorders	
Constipation	5 (2.4%)
Nausea	3 (1.5%)
Diarrhea	2 (1.0%)

MedDRA SOC or PT	PSMA-617-01 (n=206) n (%)
Blood and lymphatic system disorders	
Anemia	5 (2.4%)
Bicytopenia	2 (1.0%)
Renal and urinary disorders	
Hematuria	3 (1.5%)
Neoplasms benign, malignant, and unspecified	
Metastases to meninges	2 (1.0%)
Vascular disorders	
Hot flush	2 (1.0%)

Source: PSMA-617-01 clinical study report, Table 5.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients, PT = preferred term, SOC = system organ class
Note: The numbers in this table refer to patients not events.

In PSMA-617-01, investigator-assessed relatedness was possibly related for two events (asthenia, constipation), probably related for one event (hot flush), and definitely related for two events (cognitive disorder, injection site warmth), each in a separate patients. The Sponsor considered the asthenia, constipation, and hot flush events as unlikely related, cognitive disorder as possibly related, and injection site warmth as definitely related.

Two AEs were reported in one patient in BCR-RET-01, blood bilirubin increase and vascular access complication. Severity was listed as asymptomatic. They were assessed as unrelated by the Investigator and Sponsor.

Accounting for the greater severity of disease in patients enrolled in PSMA-617-01, the observed adverse event profile is similar to that reported in the safety studies for Ga 68 gozetotide injection approved under NDA 212642 and NDA 212643.

Laboratory Findings

Up to six patients in BCR-RET-01 had both pre- and post-Ga 68 gozetotide administration measurement of laboratory results within 1 week. While no safety signal was identified from these data, assessment is very limited by the small sample size.

Vital Signs

Up to 20 patients in BCR-RET-01 had both pre- and post-Ga 68 gozetotide administration measurement of vital signs within 1 week. While no safety signal was identified from these data, assessment is very limited by the small sample size.

Electrocardiograms (ECGs)

No paired pre- and post-Ga 68 gozetotide administration ECG results were collected.

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QT

No formal QT study was performed. Such a study was unnecessary due to the single administration of this microdose drug.

Immunogenicity

Dedicated immunogenicity evaluation was not needed and was not performed for this single administration microdose drug.

8.2.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Clinical outcome assessment data were not collected and were not needed.

8.2.7. Safety Analyses by Demographic Subgroups

In PSMA-617-01, there was a slightly greater rate of treatment-emergent adverse events in patients who were older than 65 than those who were 65 years of age or younger (Table 19). This observation might be explained by age-related co-morbidities or by statistical variability given the relatively small number of adverse events in the study. Subgroup analyses by race or ethnicity were not considered feasible because of the number of adverse events and demographic distribution. Only males were enrolled, so subgroup analysis by sex was not performed.

Table 19. Treatment-Emergent Adverse Events in PSMA-617-01, Stratified by Patient Age

Reported Events	Age ≤65	Age >65
Patients (n, % of total)	54 (26%)	152 (74%)
Adverse events (n, % of total)	16 (15%)	93 (85%)
Patients with adverse events (n, % of total)	9 (19%)	39 (81%)

Source: PSMA-617-01 clinical study report, Table 8
Abbreviations: n = number of patients or events

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies of carcinogenicity were performed, and none were needed. As with all radioactive drugs, there is believed to be a low, dose-dependent risk for induction of malignancy. Refer to Section 6 of this review for radiation dosimetry information.

Human Reproduction and Pregnancy

This product is not intended for use in females.

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Pediatrics and Assessment of Effects on Growth

This product is not intended for use in children. The Applicant proposed a waiver of pediatric studies because studies would be impossible or highly impractical. This waiver was granted, and an agreed initial pediatric study plan letter was sent on March 30, 2020.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No large overdose was described by the Applicant during the drug development program. In the absence of clinical experience to guide management of overdose, it is reasonable to recommend increasing drug clearance by hydration and, if clinically feasible, by administration of a diuretic. The main goal of such measures is to reduce patient radiation exposure. As for any overdose involving radioactive materials, the radiation effective dose to the patient should be estimated if possible. These recommendations will be included in drug labeling.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No safety signal has been identified from current postmarket experience for the approved Ga 68 gozetotide injection formulations.

Expectations on Safety in the Postmarket Setting

During development of a related PSMA-targeted PET drug, piflufolastat F 18, one patient with a history of hypersensitivity to multiple drugs and foods experienced a hypersensitivity reaction as a severe adverse event. It is possible that hypersensitivity to Ga 68 gozetotide could occur in the postmarket setting, however this possibility exists for essentially all drugs and there is no indication at this time that Ga 68 gozetotide is particularly likely to cause hypersensitivity reactions. Otherwise, as with all diagnostic tests, false positive and false negative test results could adversely affect patient management. This information will be included in labeling.

8.2.10. Integrated Assessment of Safety

Clinical safety data from studies BCR-RET-01 and PSMA-617-01 were generally compatible with the safety profile established for the approved Ga 68 gozetotide injection formulations despite the use of relatively higher gozetotide mass doses in these trials. No new safety signal was identified, and the safety profile remains reasonably benign. Risk from radiation exposure is typical of PET oncology imaging and estimated to be minimal. The potential risk of misdiagnosis from Ga 68 gozetotide PET will be managed through appropriate labeling.

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8.3. Statistical Issues

As discussed in Section 8.1, BCR-RET-01 was not considered an adequate and well-controlled study of effectiveness. Therefore, detailed statistical analysis of the efficacy results is not required.

8.4. Conclusions and Recommendations

The Applicant is relying on FDA's findings of safety and effectiveness of Ga 68 gozetotide injection under NDA 212643 to support this application for its kit for the preparation of Ga 68 gozetotide injection. A bridge was established between the kit and injection formulations. Therefore, there is sufficient evidence of efficacy of the drug for PET imaging of prostate cancer in patients with suspected metastasis who are candidates for initial definitive therapy or in whom recurrence is suspected based on elevated PSA levels. No new safety signal was identified during the Applicant's clinical development program. Thus, the review team finds the benefit of this kit to outweigh its risks and recommends approval.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultation was needed for this NDA.

10 Pediatrics

Prostate cancer incidence is essentially zero in the pediatric population. Thus, it is not possible to conduct pediatric studies for the proposed indication. On February 25, 2020, The FDA Pediatric Review Committee agreed to grant a full waiver of pediatric studies.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Because the Applicant is relying on FDA's findings of safety and effectiveness for Ga 68 gozetotide injection under NDA 212643 as the RLD, and because no new safety signal was identified in the Applicant's development program, it is recommended that the prescribing information be modified to copy the RLD prescribing information except for instructions on kit preparation, dosage forms and strengths, chemical characteristics, how supplied/storage and handling, and Applicant-specific contact information.

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12 Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not needed for this product.

13 Postmarketing Requirements and Commitment

As discussed in Section 4.2 of this review, a CMC PMC and Microbiology PMC were agreed upon with the Applicant.

The CMC PMC relates to the drug product gozetotide kit vial (PSMA-11 kit vial) and process to be implemented by the kit manufacturer. The kit vial (b) (4) limit should be set quantitatively in the specifications. A method capable of quantifying the (b) (4) content should be developed, validated, and data submitted to the application. A CMC PMC/PMR was communicated to the applicant to provide the additional data. The Applicant responded and indicated that the data will be provided by February 28, 2022.

The Microbiology PMC relates to the final radiolabeling procedure for Ga 68 gozetotide. The reconstituted gozetotide is radiolabeled at room temperature for 5 minutes with Ga 68 chloride from either a cyclotron or generator (shelf life of 12 months). (b) (4) During the review cycle, the Applicant provided sterility data for 14 product batches that were manufactured using Ga chloride eluates from generators. However, only one batch was produced using eluate from a generator that was within 1 month of expiry. A Microbiology PMC was communicated to the Applicant to provide additional sterility data for Ga 68 gozetotide product batches produced with eluates from at least three batches of each generator (Eckert and Ziegler generator and IRE generator) that are within 1 month of expiry (i.e., at least 11 months old). The Applicant responded and indicated that the data will be provided by April 29, 2022.

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14 Division Director (Clinical) Comments

I concur with the unanimous recommendation by the review team for approval Ga 68 gozetotide prepared by the Applicant's kit.

I note the Applicant's proposal to rely on FDA's findings of effectiveness for Ga 68 gozetotide injection in NDA 212643, and I concur with the reviewers' determination that BCR-RET-01 is not an adequate and well-controlled efficacy study.

I concur that the Applicant has demonstrated comparability of their product to the listed drug by the following methods: comparison of physiochemical properties and comparison of PSMA-specific cell binding and internalization in vitro; comparison of pharmacokinetics, biodistribution, and dosimetry in three healthy subjects; evaluation of the relationship between gozetotide mass dose and clinical imaging performance.

Given the adequate bridge to the listed drug, Ga 68 gozetotide prepared by the Applicant's kit is indicated for imaging of prostate cancer in men with suspected metastasis who are candidates for initial definitive therapy and in men with suspected recurrence based on elevated serum PSA.

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15 Appendices

15.1. References

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15.2. Financial Disclosure

No studies submitted in this application meet the definition of covered clinical study in 21 CFR 54.2 (e).

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