CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216023Orig1s000

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)(1)
Application Number	216023
Priority or Standard	Standard
Submit Date	May 25, 2022
Received Date	May 25, 2022
PDUFA Goal Date	May 25, 2023
Division/Office	Imaging and Radiation Medicine / Specialty Medicine
Review Completion Date	May 25, 2023
Established/Proper Name	Flotufolastat F 18
(Proposed) Trade Name	Posluma
Pharmacologic Class	Radioactive diagnostic agent
Code name	rh-PSMA-7.3 F 18
Applicant	Blue Earth Diagnostics Ltd
Dosage form	Injection
Applicant proposed Dosing Regimen	296 MBq (8 mCi) administered as an intravenous bolus injection
Applicant Proposed Indication/Population	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	254900004 | Carcinoma of prostate (disorder)
Regulatory Action	Approval
Indication(s)/Population(s)	POSLUMA 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	296 MBq (8 mCi) administered as an intravenous bolus injection

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Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; DRM, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; ADL, Associate Director of Labeling

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
M1	distant metastatic disease
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N1	regional lymph node disease
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PC	prostate cancer
PD	pharmacodynamics
PET	positron emission tomography
PI	prescribing information
PK	pharmacokinetics
PLND	pelvic lymph node dissection
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPV	positive predictive value

PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
REMS	risk evaluation and mitigation strategy
RP	radical prostatectomy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SoT	standard of truth
SPECT	single-photon emission computerized tomography
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Flotufolastat F 18, also termed rhPSMA-7.3 F 18 in the scientific literature and Posluma as the proprietary name, is a positron-emitting radiopharmaceutical that binds to prostate-specific membrane antigen (PSMA), a protein that is overexpressed in prostate cancer (PC). The recommended indications are for positron emission tomography (PET) imaging of PSMA positive lesions in men with suspected PC metastasis who are candidates for initial definitive therapy, or in men with suspected PC recurrence based on elevated serum prostate-specific antigen (PSA) level. Flotufolastat F 18 is intended to be administered at a dose of 8 mCi (296 MBq) as a bolus intravenous injection. Flotufolastat F 18 is a new molecular entity. New drug application (NDA) 216023 for flotufolastat F 18 was submitted under the 505(b)(1) pathway.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was submitted that demonstrates the ability of flotufolastat F 18 to image PC in two populations: 1) men with suspected metastases who are candidates for initial definitive therapy, and 2) men with suspected recurrence based on elevated serum PSA. Main support for efficacy was derived from two adequate and well-controlled trials that were mutually supportive and conducted prospectively by the Applicant.

The first trial (BED-PSMA-301 or LIGHTHOUSE) was a multi-center, single-arm study that evaluated the detection of regional lymph node disease (N1) in patients with newly diagnosed unfavorable intermediate-risk, high-risk, or very high-risk PC who were candidates for radical prostatectomy (RP) with pelvic lymph node dissection (PLND). The standard of truth (SoT) comparator was histopathology from the PLND. The co-primary endpoint of patient-level sensitivity for detection of N1 disease ranged from 22.9% (95% confidence interval (CI): 13.7%, 34.4%) to 30.0% (95% CI: 19.6%, 42.1%) across readers. The co-primary endpoint of patient-level specificity for detection of N1 disease ranged from 92.9% (95% CI: 88.8%, 95.9%) to 96.9% (95% CI: 93.7%, 98.7%) readers.

The second trial (BED-PSMA-302 or SPOTLIGHT) was a multi-center, single-arm study that evaluated the detection of PC lesions in men with suspected recurrence based on elevated serum PSA levels (henceforth known as biochemical recurrence or BCR) who were being considered for curative-intent salvage treatment. The SoT comparator was a composite of histopathology and imaging. The co-primary endpoint of patient-level correct detection rate (CDR) ranged from 48.3% (95% CI: 43.3%, 53.4%) to 50.9% (95% CI: 45.8%, 56.0%) across the three readers. The co-primary endpoint of region-level positive predictive value (PPV) ranged from 46.2% (95% CI: 42.0%, 50.3%) to 60.3% (95% CI: 55.1%, 65.5%) across the three readers.

Both BED-PSMA-301 and BED-PSMA-302 failed to meet one of two pre-specified co-primary diagnostic performance endpoints. However, as discussed elsewhere in this review, the

effectiveness and clinical utility of flotufolastat F 18 PET were still evident in the investigated patient populations of these two mutually supportive trials.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Flotufolastat F 18 is a positron-emitting radiopharmaceutical that binds to PSMA and is intended for imaging of PSMA positive lesions in men with suspected PC metastasis who are candidates for initial definitive therapy, or in men with suspected PC recurrence based on elevated serum PSA level. The collective data submitted by the Applicant to support approval including the results of two adequate and well-controlled trials conducted by the Applicant support approval of this NDA.

Worldwide, PC was the second most frequent cancer and the fifth leading cause of death in men in 2020 (Cancer Today, 2020). It was also the most commonly diagnosed cancer in men in more than half of the countries in the world. In addition to the significant mortality associated with PC, there is substantial morbidity caused by the disease as well as with standard treatment. Serum PSA testing is performed to detect early, asymptomatic disease, and diagnosis of cancer is confirmed with a prostate biopsy. Imaging is used to stage PC and to stratify patients, and the presence of disease in lymph nodes or distant sites can drastically alter management for a patient. Though new imaging modalities and agents have been developed over the years, such as multiparametric magnetic resonance imaging (MRI) and ^{11}C-choline and ^{18}F-fluciclovine PET, imaging is still suboptimal for PC. Recurrence of PC occurs in 27 to 53% (Artibani, Porcaro, De Marco, Cerruto, & Siracusano, 2018) of men after definitive treatment for what was deemed to be localized disease per imaging, suggesting that extraprostatic disease is frequently missed by available imaging modalities. In addition, sites of disease are often undetectable on available imaging in men who experience a BCR due to the small size of recurrent lesions. There is an unmet need for better imaging of this disease.

BED-PSMA-301 (LIGHTHOUSE) evaluated the performance of flotufolastat F 18 in men with newly diagnosed PC before definitive treatment and the data submitted demonstrates low sensitivity but high specificity of the drug for identifying metastases in pelvic lymph nodes, which is typical of PET radiotracers in this class, and suggests better performance with higher risk disease. However, with a PPV rate higher than the prevalence of lymph node metastases in the population of intended use, flotufolastat F 18 demonstrates added diagnostic value in the patients with positive flotufolastat F 18 PET scans despite low sensitivity. Flotufolastat F 18 may also identify prostate cancer lesions that are missed on standard conventional imaging and can therefore alter treatment.

BED-PSMA-302 (SPOTLIGHT) evaluated the performance of flotufolastat F 18 in men with suspected BCR and demonstrated favorable correct detection of recurrent lesions. The nature of the disease and the clinical trial design did not allow for assessment of sensitivity and specificity, which are the more traditional indicators of performance. Thus, PPV for identifying disease in a specific region was used. The PPV results show that lesions identified on flotufolastat F 18 PET imaging are likely to represent true recurrent disease. Though the true prevalence of recurrent disease is difficult to assess in this population, if the CDR of other PSMA PET imaging trials is used as the true prevalence rate, then flotufolastat

F 18 appears to add diagnostic value since its PPV rate is higher than this estimated prevalence. Detection and localization of recurrent disease can dramatically alter management in this patient population since recurrent disease in the prostate or prostatic fossa can potentially be salvaged with definitive treatment. Though disease outside the pelvis is typically treated with systemic therapy, there may be a role for ablative treatment of oligometastatic disease which would require precise localization by imaging. The performance of flotufolastat F 18 PET in the recurrent setting supports its use in patients prior to definitive therapy, and vice versa.

For safety evaluation of flotufolastat F 18, data from a total of 757 PC patients from BED-PSMA-301, BED-PSMA-302, as well as a phase 1, prospective trial (BED-PSMA-101), and 6 healthy volunteers from the BED-PSMA-101 trial were analyzed. Treatment emergent adverse events were not common and were typically mild. One treatment emergent serious adverse event was documented that resulted in a patient's death but was determined to not be related to flotufolastat F 18. Radiation effective dose from flotufolastat F 18 is typical of other PET oncology imaging agents and is estimated to impart minimal additional stochastic risk in this patient population. The mass dose of the drug is in the microgram range (<100 µg/patient). Risks of misdiagnosis related to false negative or false positive results are applicable to imaging diagnostic agents as a group, and are addressed through labeling, including strengthened warnings and precautions for patients with PC recurrence.

Overall, the potential benefit of flotufolastat F 18 in the indicated PC populations outweigh the acceptably low risks. Approval of this application is justified.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PC is the most common cancer in American men and the second leading cause of cancer-related death in this population. • The course of PC varies widely. While many men will have slow growing cancer that needs no treatment, others will have aggressive disease that leads to pain, debilitation, and death. • The pelvic lymph nodes are typical sites of local/regional spread. • Proper management of PC involves assessment of the risk of aggressive disease as well as evaluation of the location and extent of disease. • Effective treatment of PC is dependent upon accurate and reliable detection and assessment of the extent of disease and patient	• PC is a serious condition that causes substantial morbidity and mortality. • Imaging of disease can have an important impact on patient management. • The differential expression of PSMA from tumor to non-tumor tissue supports targeted strategies in PC involving disease localization using nuclear medicine imaging.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	selection. • PSMA has been confirmed as a biological target for diagnostic imaging and therapy in PC.	
Current Treatment Options	• Many imaging techniques have been applied to PC, including ultrasound, computed tomography (CT), MRI, bone imaging using ^{99m}Tc-medronate or ^{18}F-sodium fluoride, ^{111}In-capromab pendetide single-photon emission computerized tomography (SPECT), and PET using ^{11}C-choline, ^{18}F-fluciclovine, ^{68}Ga-gozetotide, or ^{18}F-piflufolastat. The technique used varies depending on what information is needed. • For patients with newly diagnosed PC who are at intermediate or higher risk, treatment choice is influenced by whether cancer has spread to regional lymph nodes and more distant sites. Standard of care imaging has traditionally relied on ^{99m}Tc-medronate bone scan along with CT or MRI of the abdomen and pelvis to detect such metastases. The diagnostic performance of these techniques is moderate. Recurrent PC after prostatectomy has been estimated to occur in up to 30% of men who had no evidence of metastatic disease on initial conventional imaging. While therapeutic methods may be a factor, this recurrence rate suggest that disease outside the prostate gland is missed by traditional imaging technique in a number of cases. • PC recurrence is usually first recognized due to an increase in serum PSA level. Bone scan and CT or MRI are traditionally used to locate recurrent disease, because this information might guide optimal therapy. PET performed with ^{11}C-choline, ^{18}F-fluciclovine, ^{68}Ga-gozetotide, or ^{18}F- piflufolastat might also be used as they are	• Despite the availability of many different techniques for imaging prostate cancer, there is an unmet need for better diagnostic performance. • Traditional standard of care imaging in most scenarios is based largely on anatomic modalities such as CT and MRI, which are best at finding large lesions. • Functional bone imaging tends to be either insensitive at lower, clinically relevant PSA levels in the case of ^{99m}Tc-medronate or limited by low specificity in the case of ^{18}F-sodium fluoride. • ^{11}C-choline and ^{18}F-fluciclovine are PET drugs approve 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. • ^{68}Ga-gozetotide and ^{18}F- piflufolastat are PSMA-specific PET drugs recently approved for use in the initial therapy and biochemical recurrent settings. • There is an urgent need for more effective

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	specifically approved for prostate cancer imaging in the setting of biochemical recurrence. There is a need for higher detection rate when the PSA level is low. • Once patients reach the metastatic castration-resistant prostate cancer (mCRPC) stage, their expected overall survival is low, and current treatments for mCRPC provide a limited 5-year survival rate.	treatments and management strategies to improve outcomes for patients with PC. Effective treatment of PC is dependent upon accurate and reliable patient selection.
Benefit	• Two adequate and well-controlled trials were conducted by the Applicant and submitted in this NDA. • BED-PSMA-301 (LIGHTHOUSE) was a prospective, single-arm, multi-center trial that enrolled 356 patients with unfavorable intermediate-, high-, or very high-risk prostate cancer who were planned for radical prostatectomy (RP) with pelvic lymph node dissection (PLND) to determine the effectiveness of flotufolastat F 18 in identifying prostate cancer in pelvic lymph nodes and distant metastatic sites. In the 296 patients who could be evaluated, the co-primary endpoint for detection of pelvic lymph node metastases of patient-level sensitivity using histopathology as a standard of truth (SoT) was low and did not meet the pre-specified statistical threshold in all three blinded readers, while the second co-primary endpoint of patient-level specificity was high and did meet the pre-specified statistical threshold in all three blinded readers. Importantly, the patient-level PPV for pelvic lymph node metastases was higher than the prevalence of positive pelvic lymph nodes in the study population as determined by histopathology. Results from subgroup analysis demonstrated a trend towards better performance in higher risk patients. The secondary endpoint of the verified detection rate (VDR) for distant metastasis using	• Although the pre-specified sensitivity goal of BED-PSMA-301 was not met, the performance data still demonstrate clinical utility in this patient population. Low sensitivity and high specificity are typical of other PSMA PET imaging agents and characteristic of certain conventional imaging modalities; therefore, the low sensitivity of the drug is not anticipated to negatively affect standard management of these patients. However, a positive finding on flotufolastat F 18 PET may dramatically alter the choice of treatment for an individual patient.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	either histopathology or confirmatory imaging as a SoT ranged from 9.9% to 14.2%. • BED-PSMA-302 (SPOTLIGHT) was a prospective, single-arm, multi-center trial that enrolled 391 patients with BCR who were eligible for curative salvage therapy to determine the effectiveness of flotufolastat F 18 in identifying sites of recurrent disease. In the 366 patients who could be evaluated using a composite standard of truth consisting of histopathology, historical/baseline imaging, and follow-up imaging, the co-primary endpoint of patient-level CDR exceeded the pre-specified statistical threshold of 36.5% in all three blinded readers, while the second co-primary endpoint of region-level PPV was low and did not meet the pre-specified statistical threshold in all three blinded readers. The patient-level PPV in this trial demonstrated that patients with a positive flotufolastat F 18 PET scan have recurrent disease 55.5% to 71.5% of the time. There were weaknesses in the composite SoT used in this trial, but these did not seem to significantly prevent interpretation of the trial results.	• Although the pre-specified region-level PPV goal was not met in BED-PSMA-302, the data demonstrate the potential value of flotufolastat F 18 PET in the biochemical recurrence setting. Flotufolastat F 18 demonstrates a satisfactory correct detection rate, and a detected recurrent lesion could impact treatment management.
Risk and Risk Management	• The studied safety population consisted of 757 men with PC and 6 healthy volunteers. • There were no deaths related to flotufolastat F 18. • Adverse events were not common and typically mild in severity. • The radiation effective dose is estimated to be 4.2 mSv for an 8 mCi dose. • SPOTLIGHT results demonstrated that the interpretation of POSLUMA PET often differed depending on imaging readers with the three central readers agreeing on the presence or absence of positive lesions across evaluated regions in 30% of patients (Fleiss	• No safety concerns were identified. • The radiation effective dose is typical of other PET oncology imaging agents. • Prescribing information warnings and precautions for risk of image misinterpretation were strengthened for patients with PC recurrence.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	kappa of 0.41 [95% CI: 0.39 to 0.43]).	

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):		
☒	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

PC is the second most frequently diagnosed cancer and the fifth leading cause of death in men as estimated by the International Agency for Research on Cancer in 2020. It is typically diagnosed in men older than 65 years of age (Daniyal, et al., 2014) and is frequently asymptomatic in early stages. PC is often detected by an elevated PSA or an abnormal DRE, with prostate biopsy performed to confirm the diagnosis of cancer. The progression of PC can be highly variable; while some men have indolent disease that remains confined to the prostate for many years and never causes symptoms or problems, some men have aggressive disease that metastasizes early, causing severe morbidity and death. The aggressiveness of a particular patient's cancer can be predicted based on several factors, and this characterization is important when determining the most appropriate treatment for PC. PSA, Gleason score, and the American Joint Committee on Cancer TNM staging are all used to stratify patients into prognostic risk groups such as those developed by the widely referenced National Comprehensive Cancer Network (NCCN) (NCCN Guidelines Version 1.2023 Prostate Cancer, 2022). Other details from the prostate biopsy such as the number of cores positive, percentage of each core positive, and PSA density are also considered to classify patients into the very low-, low-, favorable intermediate-, unfavorable intermediate-, high-, and very high-risk groupings. Imaging is not specifically used to stratify patients into these risk groups, but the necessity of obtaining imaging is determined from the grouping, once a certain risk threshold has been exceeded.

PC spreads throughout the body in a fairly typical pattern as the disease progresses. Once leaving the prostate gland, spread is most commonly to the pelvic lymph nodes; disease that has spread here is termed regional metastasis or N1 disease. PC then spreads beyond the pelvis into extrapelvic lymph nodes, such as the abdominal retroperitoneal lymph nodes, and skeleton, which is the most common site of distant metastatic disease. As the cancer progresses, other organs can be involved as well including the lung and liver.

PC that is localized to the prostate gland but with a relatively elevated risk of disease progression can be treated with curative intent therapy such as radical prostatectomy or radiation therapy with high success rates (Mohler, et al., 2019). Therefore, detecting disease outside of the prostate gland in these patients is important because it can change management. After definitive treatment, PSA levels are expected to fall to undetectable levels in patients treated with prostatectomy and to a nadir value in patients treated with radiation. Monitoring of PSA levels is of primary importance when following patients for recurrence; patients with rising PSA levels after definitive therapy are likely to have recurrent disease and are said to have biochemical recurrence. Optimal treatment in this setting is dependent on recurrent disease location and extent. Potentially curative salvage treatment may be offered to patients with disease localized to the prostate gland or prostate fossa, such as radiotherapy, surgery, cryotherapy, or high-intensity focused ultrasound. For recurrent disease in distant

sites, non-curative systemic therapy is commonly used, though there is an emerging role for radiotherapy or other ablative techniques to treat oligometastatic disease. Accurate localization of disease in the recurrent setting is therefore also of importance and has substantial implications on treatment choice.

Currently available imaging modalities have variable performance in PC; there is a need for advancement in diagnostic imaging for this malignancy. PET radiotracers that specifically bind to PSMA have been developed, and efficacy data from approved PSMA PET radiotracers indicate possible improved performance compared to conventional imaging modalities such as CT, MRI, or bone scan (Bouchelouche & Choyke, 2018).

Flotufolastat F 18 is a PET imaging agent that targets PSMA on PC cells. PSMA is a transmembrane glycoprotein that is overexpressed in most PC cells (Israeli, Powell, Corr, Fair, & Heston, 1994) (Silver, Pellicer, Fair, Heston, & Cordon-Cardo, 1997) (Osborne, et al., 2013) when compared to benign prostatic epithelium; this differential expression of PSMA between PC cells and non-PC tissue provide the basis for use of this glycoprotein as a molecular target. There also appears to be a correlation with the level of PSMA expression on prostate cancer cells and higher grade of disease (Silver, Pellicer, Fair, Heston, & Cordon-Cardo, 1997).

2.2. Analysis of Current Treatment Options

Imaging options for PC are listed in Table 1 below. Efficacy estimates presented in the table are not meant to be directly compared since the populations and trial designs in which these performance numbers were obtained were different. Ultrasound, CT, and MRI are general anatomic imaging techniques used in many clinical settings and in various malignancies. ^{99m}Tc-medronate SPECT and ^{18}F-sodium fluoride PET imaging are used for general imaging of bone lesions and are non-specific. On the other hand, ^{111}In-capromab pendetide, ^{11}C-choline, ^{18}F-fluciclovine, ^{68}Ga-gozetotide, and ^{18}F-piflufolastat are PC specific imaging agents, the last two being PSMA-targeted PET radiotracers in the same class as flotufolastat F 18. Screening for PC with any imaging modality is not currently recommended.

Table 1. Prostate Cancer Imaging Techniques

Technique	Use in Practice	Efficacy	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%	Current best choice for imaging prostate gland

Technique	Use in Practice	Efficacy	Comments
		(using DWI)	
^{99m}Tc-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
^{18}F-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
^{111}In-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 the market by BLA holder
^{11}C-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
^{18}F-fluciclovine	Restaging	Identifying disease after BCR: PPV 76%	Approved for PET imaging of prostate cancer only in the BCR setting
^{68}Ga-gozetotide	Initial staging Restaging Patient selection for lutetium Lu 177 vipivotide tetraxetan therapy	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 47% Specificity 74% Identifying disease after BCR: Patient-level PPV 72% Patient selection: i) OS 15.3 months (therapeutic plus imaging agent plus BSoC) vs. 11.3 (imaging agent plus BSoC); ii) Imaging agent inter-reader Fleiss kappa 0.6; iii) exploration of therapeutic effect in relation to imaging	PSMA-targeted

Technique	Use in Practice	Efficacy	Comments
^{18}F-piflufolastat	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 28-39% Specificity 95-98% Identifying disease after BCR: Patient-level PPV 78-81% Region-level PPV 67-70%	PSMA-targeted

Source: Adapted from Multi-disciplinary Review and Evaluation for NDA 215841
Abbreviations: BCR, biochemical recurrence; BSoC, best standard of care; BLA, biologics license application; CT, computed tomography; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; OS, overall survival; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; SPECT, single photon emission computed tomography

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Flotufolastat F 18 is a new molecular entity that is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant submitted a pre-IND Type B meeting request to the FDA on 10/19/2018 to discuss the development program for ^{18}F-rhPSMA-7.3, the prior name for flotufolastat F 18, and to gain agreement on the format and content of a proposed NDA submission. A written response to this request recommended at least one prospective, multi-center trial for evaluation of efficacy and safety in the patient population of intended use where the primary endpoint is compared against a reference standard instead of reliance on retrospective chart review and literature review.

A Type C meeting was held on 6/19/2019, where the FDA recommended against a (b) (4) (b) (4) comparator design for a phase 3 trial in the BCR setting. The FDA recommended performance metrics of detection rate verified against a composite truth standard consisting of histopathology and longitudinal imaging, and PPV (defined as TP/TP+FP). For the proposed phase 3 study in primary PC, the FDA recommended against focusing on identification of patients with M1 disease and on evaluating sensitivity and specificity for detection of N1 lesions against pathology from RP and PLND.

In a Type A meeting request written response dated 9/6/2019, the co-primary endpoints of patient-level CDR and region-level PPV were recommended for BED-PSMA-302. FDA agreed that the proposed 65% lower bound of the 95% CI would be an acceptable success threshold for PPV.

The protocol for BED-PSMA-301 was submitted on 9/27/2019 to open IND 141561, and a safe to proceed letter was issued on 10/24/2019. The protocol for BED-PSMA-302 was submitted

11/4/2019. Of note, the Applicant increased the sensitivity and specificity thresholds to 22.5% and 82.5%, respectively, for BED-PSMA-301 in a subsequent amendment based on non-hold recommendations to increase the thresholds to 25% and 85%. The Applicant also changed the co-primary endpoint for BED-PSMA-302 from patient-level PPV to region-level PPV and also increased emphasis on longitudinal image assessments as part of the composite reference standard as recommended in non-hold comments.

A pre-NDA meeting was held on 4/9/2021, where the Applicant discussed the difficulty with conducting studies during the COVID pandemic, which resulted in delayed completion of the trials, particularly BED-PSMA-301. The Applicant's plan to rely on BED-PSMA-302 data with additional evidence for support of an NDA application for an indication only in the BCR setting was also discussed. No efficacy results from BED-PSMA-302 were presented at the meeting, and without this information the FDA was unable to provide feedback on the strength of the approach suggested by the Applicant.

NDA 216023 for flotufolastat F 18 was submitted on 12/22/2021, with complete data for BED-PSMA-302, but only safety data from BED-PSMA-301 for a subset of patients and no efficacy data from BED-PSMA-301. After discussion with the FDA, the Applicant elected to withdraw NDA 216023 on 2/17/2022. The NDA was resubmitted on 5/25/2022 with complete data from both studies. It was filed on 7/22/2022. Priority review designation was requested, but a standard review classification was granted given availability of other products in this class.

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

4.1. Office of Scientific Investigations (OSI)

Although there were no specific data integrity issues suspected with respect to efficacy and safety, an OSI audit was requested and performed because BED-PSMA-301 and BED-PSMA-302 provided the principal data used for regulatory decision making. Three clinical investigators at three different clinical sites were inspected due to high patient enrollment, and the contract research organization, (b) (4) was also inspected because it handled the central PET imaging read results. There were no significant good clinical practice (GCP) violations found, and the two studies appear to have been conducted in compliance with GCP principles and regulations. OSI determined that the data for the studies from the four GCP inspections performed appear acceptable to support this NDA.

4.2. Product Quality

The quality review team had a final overall approval recommendation and provided the following rationale. Summarizing over all components (drug substance, drug product, manufacturing and facilities, microbiology, and labeling), all deficiencies identified are resolved and there is nothing left pending. All manufacturing facilities (31 of PETNET within the USA) that

will produce Posluma under NDA 216023 (resubmission) have been found acceptable and approved for [redacted] (b) (4) final PET Drug.

For additional information, see the Integrated Quality Assessment finalized May 16, 2023.

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

This NDA can be approved from a nonclinical perspective.

Flotufolastat F18 (a.k.a radiohybrid (rh) prostate-specific membrane antigen (PSMA)-7.3; rhPSMA-7.3 F 18) is a radiopharmaceutical PET imaging agent that binds with high affinity to the extracellular epitope of PSMA. The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an F 18-radiolabeled silicon fluoride acceptor moiety, and a gallium chelator complex. PSMA is overexpressed by most prostate cancers. Flotufolastat F 18 It is one of four diastereoisomers (7.1 – 7.4) making up rhPSMA-7 F 18.

The Applicant conducted nonclinical pharmacology and PK/ADME studies of flotufolastat to support the submission. Studies were conducted with rhPSMA-7 F 18 and individual diastereoisomers that evaluated PSMA binding, off-target binding, tumor cell uptake, and biodistribution in xenograft transplant mice. Biodistribution and pharmacokinetic data demonstrated greatest uptake of flotufolastat F 18 by PSMA-expressing tissues with rapid clearance by predominately urinary excretion and minimal metabolism. Nonclinical bridging studies were conducted to evaluate the physiochemical properties of the four diastereoisomers and included biodistribution studies of C-14 labeled flotufolastat to compare tissue distribution and tumor uptake; a limited biodistribution study was conducted to compare the rhPSMA-7 F 18 mixture to flotufolastat F 18. Safety pharmacology studies were not conducted by the Applicant and are not recommended for microdose radiopharmaceuticals.

The Applicant conducted one non-GLP single-dose toxicity study and one GLP extended single-dose toxicity study of flotufolastat demonstrating safety to support the NDA application. In an extended, single-dose toxicity study in Wistar Han rats, no notable findings were reported for flotufolastat at up to 10 mg/kg, with a safety factor of 971-fold based on the intended clinical mass dose of not more than (NMT) 100 µg. Genotoxicity studies were not conducted and are

not recommended for microdose radiopharmaceuticals. Development and reproductive toxicity studies were not required for flotufolastat. The Applicant requested to omit these studies and the Agency concluded that this was acceptable based on the proposed single-use indication, target population, and microdose.

In summary, no additional nonclinical studies are necessary to support the safety of flotufolastat F 18, a microdose radiopharmaceutical, for PET imaging of PSMA-positive lesions in certain men with prostate cancer.

5.2. Referenced NDAs, BLAs, DMFs

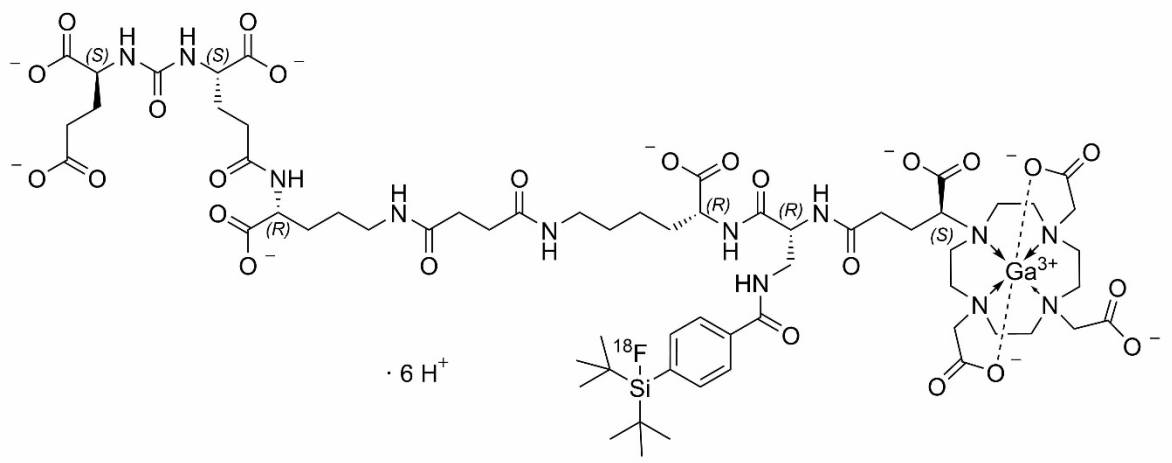
None.

5.3. Pharmacology

5.3.1. Introduction

Flotufolastat or radiohybrid (rh) prostate-specific membrane antigen (PSMA)-7.3 (also referred to as rhPSMA-7.3) is a glutamate-urea-glutamate (EuE) based inhibitor that binds to an extracellular epitope of PSMA with high affinity (IC_{50}=4.37±1.14nM); the flotufolastat structure (one of four isomers with varying affinity and cell uptake)) includes the PSMA binding motif, a peptide spacer, F 18-radiolabeled silicon fluoride acceptor moiety, and gallium chelator complex. The chemical structure of flotufolastat F 18 is shown below in Figure 1.

Figure 1. Chemical Structure of Flotufolastat F 18



Source: Applicant draft prescribing information
Molecular Formula/Molecular Weight: $C_{63}H_{96}FGaN_{12}O_{25}Si$ / 1538.3 g/mol

5.3.2. Mechanism of Action

Flotufolastat acts by binding to an extracellular epitope of glutamate carboxypeptidase II, also known as N-acetyl-L-aspartyl-L-glutamate peptidase I, NAAG peptidase, or PSMA. The F 18-radiolabeled drug product flotufolastat F 18, through the EuE ligand, binds to PSMA and is internalized by PSMA-overexpressing prostate cancer cells, permitting PET imaging. PSMA expression has been shown to correlate with prostate cancer aggressiveness (Rowe, et al., 2016).

5.3.3. Primary Pharmacology Studies

The Applicant conducted a series of binding and cellular uptake studies (Study BEDPSMADEV001) to characterize the physiochemical properties of rhPSMA-7 isomers, rhPSMA-7.1 through rhPSMA-7.4, and bridge prior PET imaging studies that were conducted with the racemic mixture to a single isomer. Biodistribution studies of rhPSMA-7 isomers in PSMA overexpressing tumor (LNCaP) bearing mice are not reviewed here. All four of the diastereoisomers bound PSMA with high nanomolar affinity with IC_{50} values ranging from 3.6 to 6.9nM (IC_{50} for 7.1=6.85±1.36; IC_{50} for 7.2=3.70±1.01; IC_{50} for 7.3=4.37±1.14; IC_{50} for 7.4=3.62±0.65) with comparable LogP values (-3.46±0.29 and -3.26±0.19 for rhPSMA-7 and rhPSMA-7.3, respectively). Cell internalization was compared to reference PSMA ligand, [I 125]-I-BA)KuE in a PSMA-overexpressing cell line, LNCaP [without and with 2-(phosphonomethyl)pentanedioic acid or PMPA], and ranged from 69.6±5.2% to 207.3±4.1% internalization (69.6±5.2 for 7.1, 191.8±15.5 for 7.2, 161.4±8.9 for 7.3, and 207.3±4.1 for 7.4). Based on the results of Study # BEDPSMADEV001, rhPSMA-7.3 F 18, the most abundant diastereoisomer in the rhPSMA-7 F 18 mixture, was selected as the single diastereoisomer for further clinical development.

Table 2. Diastereoisomer Comparison for rhPSMA-7 in Study BEDPSMADEV001

	rhPSMA-7 (^{18}F)[a]	rhPSMA-7.1 (^{18}F)	rhPSMA-7.2 (^{18}F)	rhPSMA-7.3 (^{18}F)	rhPSMA-7.4 (^{18}F)
Typical retention time (minutes)	NA	31.6	28.3	28.9	30.1
Typical percentage of whole mixture (%)	100	21[b]	22[b]	37[b]	20[b]
Mean IC_{50} (±SD; nM)	3.0 (0.7)[c]	6.9 (1.4)	3.7 (1.0)	4.4 (1.1)	3.6 (0.7)
Mean internalization rate (±SD; % of [^{125}I]IB-KuE)	126 (13)[c]	70 (5)	192 (16)	161 (9)	207 (4)
Lipophilicities (octanol-water distribution coefficient; Mean log D[d] [±SD])	-3.5 (0.3)	-3.1 (0.3)	-3.1 (0.2)	-3.3 (0.2)	-3.3 (0.2)
HSA binding (%)	96.7	97.7	97.8	96.9	96.6

Abbreviations: ^{18}F=fluorine-18; ^{125}I=iodine-125; HSA=human serum albumin; IC_{50}=half maximal inhibitory concentration; PBS=phosphate buffered saline; PSMA=prostate-specific membrane antigen; rh=radiohybrid; SD=standard deviation.

[a] rhPSMA-7 (^{18}F) is a diastereoisomeric mixture that contains four diastereoisomers, identified as rhPSMA-7.1 (^{18}F), rhPSMA-7.2 (^{18}F), rhPSMA-7.3 (^{18}F) and rhPSMA-7.4 (^{18}F), of which rhPSMA-7.3 is the most abundant.

[b] The exact amount can vary for each diastereoisomer (e.g. for rhPSMA-7.3 (^{18}F) values of ~25-35% were reported depending on production).

[c] Not reported in Study BEDPSMADEV001 but reported in Wurzer et al., 2020a and/or Wurzer et al., 2020b.

[d] Determination of the log D values was carried out in PBS (pH 7.4) and *n*-octanol (= log $D_{oct/PBS}$). Per Study BEDPSMADEV001 Erratum dated 02 July 2021, throughout the study report reference is made to lipophilicity determinations as the partition coefficient (log P). The quoted values are correct but all values reflect the distribution coefficient (log D) not log P.

Source: Applicant Table 2 in Module 2.6.2 Pharmacology Written Summary

5.3.4. Secondary Pharmacology Studies

Secondary pharmacology studies were limited to an in vitro pharmacology study (Study 100045872) that assessed potential off-target activity of flotufolastat (5 µg/mL) against a panel of 44 potential targets including receptors, enzymes, and transporters. In the screening assay, inhibition or stimulation greater than 50% were considered to represent a biologically significant effect. Based on the results of the screening study, flotufolastat had no activity against any of the 44 targets evaluated and not likely to demonstrate pharmacologic activity at the proposed clinical dose of NMT 100 µg.

5.3.5. Safety Pharmacology

Safety pharmacology studies of flotufolastat were not conducted and are not needed for a microdose radiopharmaceutical based on current CDER guidance.

5.4. ADME/PK

Table 3. ADME/PK Study Findings

Type of Study	Major Findings
Absorption	N/A; administration is intravenous
Distribution	
[^{14}C]-rhPSMA-7.3: Absorption, Distribution, Metabolism, and Excretion in the Rat Following Intravenous Administration (8391458)	Mean exposure by $AUC_{0-\infty}$ was 15,900 ng equiv.h/g with a mean half-life of 9.5 hr (terminal elimination phase) following a single bolus injection of rhPSMA-7.3 C14 equivalent to a 3.7 mg/kg dose level. V_d was 3,270 mL/kg, suggesting substantial tissue distribution (total body water of rat is approximately 670 mL/kg). Highest organ exposure to C 14 labeled flotufolastat were the kidney corticomedullary junction, cortex, and medulla based on rapid urinary elimination. Uptake greater than plasma was observed in the bile ducts, spleen, liver, adrenal cortex and medulla, cecum mucosa, bone surface, pituitary, tooth pulp, penis, mucus gland, choroid plexus, and thyroid. Organs that demonstrated lowest exposure include the bone mineral, muscle, cerebrospinal fluid, seminal vesicles, meninges, cartilage, white fat, CNS, vitreous humor, and lens.
^{18}F-radiohybrid-PSMA-7 (1 8F-rhPSMA-7): A SiFA- and DOTAGA-Based Inhibitor for PET Imaging of Glutamate Carboxypeptidase II Expression. Preclinical Evaluation of ^{18}F-rhPSMA-7 and Isomers ^{18}F-rhPSMA-7.1, ^{18}F-rhPSMA-7.2, ^{18}F-rhPSMA-7.3 and ^{18}F-rhPSMA-7.4 (BEDPSMADEVOO1)	Biodistribution and radiation dosimetry of rhPSMA-7 F 18 isomers 7.1 through 7.4 were evaluated in male severe combined immunodeficiency (SCID) mice (6 – 8 weeks of age, <0.2 nmol test article). Radioactivity distribution of rhPSMA-7 F 18 diastereoisomers were comparable for most tissues examined. Diastereoisomers 7.1 and 7.3 trended to show slightly greater relative tumor accumulation compared to diastereoisomers 7.2 and 7.4 but may also have been due to experimental variability.

Type of Study	Major Findings
Distribution and Excretion Following Single Intravenous Administration of ^{18}F-rhPSMA-7 and ^{18}F-rhPSMA-7.3 in Mice (BEDPSMADEV002)	Biodistribution and radiation dosimetry of rhPSMA-7 F 18 and rhPSMA-7.3 F 18 were evaluated in male severe combined immunodeficiency (SCID) mice (6 – 7 weeks of age, 100 pmol test article by intravenous bolus). Radioactivity of rhPSMA-7 F 18 and rhPSMA-7.3 F 18 rapidly accumulated in the kidney, spleen, lung, liver, and heart with gradual elimination by the kidney, the radiation dose-limiting organ and the main excretion route. The extrapolated total effective doses were 0.0266 (3.5 hr bladder-voiding interval) and 0.0122 (1 hr bladder-voiding interval) mSv/MBq for rhPSMA-7 F 18 and 0.0217 and 0.0128 mSv/MBq for PSMA-7.3 F 18. Based on a 1 hr bladder voiding interval and 370 MBq (10 mCi) radiation dose, the effective dose would be less than 5 mSv and similar between rhPSMA-7 F 18 and rhPSMA-7.3 F 18.
rhPSMA-7.3: In Vitro Binding to Rat and Human Plasma Proteins (8391453)	In vitro, rhPSMA-7.3 was stable in rat and human plasma up to 6 hr; rhPSMA-7.3 bound moderately to plasma proteins of rat (75.2±2.1) and human plasma (82.4±0.3) and binding was independent of concentration.
Metabolism	
[^{14}C]-rhPSMA-7.3: Absorption, Distribution, Metabolism, and Excretion in the Rat Following Intravenous Administration (8391458)	rhPSMA-7.3 C 14 underwent limited metabolism with the principal moiety corresponding to the parent compound by retention time which declined over time. The same moiety was also present in urine and feces, accounting for approximately 62% and 10% of the administered radioactivity, respectively. The principal metabolite in plasma (P5) had a retention time equivalent to approximately half that of the parent, with concentrations declining over the course of the study; P5 metabolite was also present in urine and feces, accounting for 3.7% and 1.2% of administered radioactivity, respectively.
rhPSMA-7.3: Identification of the Responsible Enzymes for Metabolism of rhPSMA-7.3 (8391457)	In vitro, rhPSMA-7.3 metabolism was evaluated by incubation with pooled human liver microsomes, pooled human liver S9 fraction, recombinant cytochrome P450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP21, CYP3A4), and UDP glucuronosyltransferase enzymes (UGT1A1, UGT2B7). Under the conditions of this in vitro study, rhPSMA-7.3 was metabolically stable (>90% parent compound remaining) for up to 1 hr and no additional components or metabolites were observed.

Type of Study	Major Findings
Excretion	
[^{14}C]-rhPSMA-7.3: Absorption, Distribution, Metabolism, and Excretion in the Rat Following Intravenous Administration (8391458)	rhPSMA-7.3 C 14 clearance (238 mL/h/kg) was low relative to mean blood flow in liver and kidney (approximately 3300 and 2200 mL/h/kg, respectively), indicating passive elimination of test substance-related radioactivity. Elimination was principally via the renal route (approximately 83%) with evidence of biliary elimination and excretion in the feces (approximately 15%).
TK Data from General Toxicology Studies	
rhPSMA-7.3: Extended Single-Dose Intravenous (Bolus) Administration Toxicity Study in the Rat Followed by a 2-Week Observation Period (8391451)	There were no significant differences in the TK parameters calculated for male and female rats. Systemic Exposure: Systemic exposure by C_{max}, AUC_{0-t}, and AUC_{0-24} increased with increasing dose in a dose proportional manner (0.1 to 10 mg/kg) and was similar between sexes. The NOAEL for flotufolastat under the conditions of the study was considered by the reviewer as 10 mg/kg. Systemic exposure by C_{max} and AUC_{0-t} at the NOAEL was 139 µg/mL and 62.0 h.µg/mL, respectively for males, and 156 µg/mL and 60.7 h. µg/mL, respectively for females.
TK Data from Reproductive Toxicology Studies *Study not conducted*	N/A
TK Data from Carcinogenicity Studies *Study not conducted*	N/A

Source: Reviewer's analysis
Abbreviations: ADME, absorption, distr bution, metabolism, excretion; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum observed plasma concentration; NOAEL, no observed adverse effect level; PK, pharmacokinetics; rhPSMA-7.3, radiohybrid prostate-specific membrane antigen-7.3; $t_{1/2}$, half-life; TK, toxicokinetic; T_{max}, time to maximum plasma concentration; V_d, volume of distribution.

5.5. Toxicology

5.5.1. General Toxicology

The rat was selected as the single species for the flotufolastat toxicology program. The clinically relevant route of exposure (IV injection) was used for the in vivo toxicology studies, which was limited to one non-GLP single-dose toxicity study (Study 8391452) and one GLP extended, single-dose toxicity study (Study 8391451). Single-dose IV (bolus) toxicity studies were conducted with flotufolastat formulated in phosphate-buffered saline (PBS [pH 7.4]) vehicle at up to 10 mg/kg in Crl: WI (Han) rats.

For the non-GLP dose range-finding single dose toxicity study (Study 8391452), rats were treated with 0, 0.5 (low dose, LD), 5 (mid dose, MD), or 10 (high dose, HD) mg/kg flotufolastat by IV administration and evaluated for signs of toxicity by mortality, clinical signs, body weight, and clinical pathology parameters. Study animals were euthanized and necropsied on Day 8 and

there were no test article-related findings in rats at up 10 mg/kg. For GLP Study 8391451, rats were treated with 0, 0.1 (low dose, LD), 1 (mid dose, MD), or 10 (high dose, HD) mg/kg flotufolastat by IV administration and evaluated for signs of toxicity by mortality, clinical signs, and body weight, as well as clinical pathology (hematology, coagulation, clinical chemistry), macroscopic pathology, and histopathology findings. Main study and recovery animals were euthanized and necropsied on Day 2 and Day 15, respectively. There were no test article-related findings in rats administered flotufolastat at up to 10 mg/kg, the highest dose level tested. The absence of nonclinical findings supports the safety for a single intravenous administration of flotufolastat F 18 based on the proposed clinical mass dose of NMT 100 µg (1.67 µg/kg assuming a 60 kg body weight) with an adequate safety factor (971-fold based on body surface area scaling).

Study title/ number: rhPSMA-7.3: Single-Dose Intravenous (Bolus) Administration Toxicity Study in the Rat/ 8391452

- Flotufolastat was not associated with any dose-related clinical findings, and all rats survived to scheduled necropsies. Based on the absence of any toxicologically relevant findings, the NOAEL was 10 mg/kg (the highest dose tested).
- No flotufolastat-treated animals died following a single IV injection and there were no test article-related clinical observations, effects on body weight or body weight change, or effects on food consumption throughout the study.
- Clinical pathology findings were limited to increased WBC counts in male (MD and HD for neutrophils and lymphocytes) and female animals (LD, MD, HD for neutrophils only) that lacked dose dependence, as well as increased urea levels in male (MD and HD) and female animals (HD only). Findings were not considered to be toxicologically relevant due to small sample size, lack of dose dependence, and lack of corresponding macroscopic or histopathologic changes.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: No

Table 4. Methods, Study 8391452

Methods	Details
Dose and frequency of dosing:	0 (vehicle), 0.5 (LD), 5 (MD), 10 (HD) mg/kg rhPSMA-7.3; single-dose administration
Route of administration:	Intravenous
Formulation/Vehicle:	Drug product was formulated as a solution in phosphate buffered saline (rhPSMA-7.3: Lot #: 180810_7, 180810_8, % Purity: >99%)/ Phosphate buffered saline), pH 7.4
Species/Strain:	Rat/ Crl: WI (Han)
Number/Sex/Group:	3/sex/group
Age:	6 – 7 weeks at dosing
Satellite groups/ unique design:	None

Deviation from study protocol affecting interpretation of results:	No

Source: Reviewer's analysis
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; rhPSMA-7.3, radiohybrid prostate-specific membrane antigen-7.3

Table 5. Observations and Results: Changes From Control, Study 8391452

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	No significant test article-related findings.
Body weights	No test article-related effects on body weights or body weight gains.
Hematology	In males, increased total WBC counts (40% and 21% in MD and HD, respectively); increased neutrophils (42% and 33% in MD and HD, respectively) and lymphocytes (40% and 21% in MD and HD, respectively). In females, increased neutrophil counts for all dose levels (165%, 212%, and 175% for LD, MD, and HD, respectively). The statistically significant findings in the context of the single-dose toxicity study were not considered to be toxicologically relevant based on the small samples size (n=3/sex/group), lack of dose dependence, and absence of macroscopic or histopathologic findings.
Clinical chemistry	Increased urea levels in males at MD and HD (73% and 76%, respectively) and females at HD (35%); findings were not considered to be toxicologically relevant due to lack of dose dependence and absence of corresponding macroscopic or histopathologic findings.
Gross pathology	No test article-related macroscopic findings at terminal necropsy.
Organ weights	Not reported.
Histopathology Adequate battery: Yes	No test article-related microscopic findings.

Source: Reviewer's analysis
Abbreviations: HD, high dose; LD, low dose; MD, mid dose; WBC, white blood cell

5.5.2. Extended Single-Dose Toxicity

Study title/ number: rhPSMA-7.3: Extended Single Dose Intravenous (Bolus) Administration Toxicity Study in the Rat Followed by a 2 Week Observation Period/ 8391451

- Flotufolastat was not associated with any dose-related clinical findings and all rats survived to scheduled necropsies. Based on the absence of any toxicologically relevant findings, the NOAEL was 10 mg/kg (the highest dose tested). Systemic exposure (C_{max} and AUC_x) at the NOAEL was 139 µg/mL and 62 µg.h/mL, respectively, for males and 156 µg/mL and 60.7 µg.h/mL, respectively, for females. The dose margin was 971-fold the proposed clinical dose of NMT 100 µg (or 1.67 µg/kg) per administration.
- No flotufolastat-treated animals died following a single intravenous injection and there were no test article-related clinical observations, effects on body weight or body weight change, or effects on food consumption throughout the study.
- No test article related findings for clinical pathology parameters (hematology, coagulation, clinical chemistry) at up to 10 mg/kg, the highest dose tested.
- Decreased thyroid/parathyroid weight (unadjusted, body weight, and brain weight adjusted) on main study day (HD animals only) and recovery study day (MD and HD males,

HD females) was not considered to be toxicologically relevant due modest change from control and absence of corresponding macroscopic or microscopic findings.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Table 6. Methods, Study No. 8391451

Methods	Details
Dose and frequency of dosing	0 (vehicle), 0.1 (LD), 1 (MD), 10 (HD) mg/kg rhPSMA-7.3; single dose administration
Dose multiples of clinical dose	9.7x (LD), 97.1x (MD), 971x (HD)
Route of administration	Intravenous (bolus)
Formulation/Vehicle	Drug product (rhPSMA-7.3) was formulated as a sterile solution for IV injection (Lot #: AD-0002E-030, % Purity: 90.9%) / Phosphate buffered saline, pH 7.4
Species/Strain Number/Sex/Group	Rat/ Crl: WI (Han) 10/sex/group (main study) and 5/sex/group (recovery)
Age	6 – 8 weeks at dosing
Satellite groups/ unique design	TK satellite, n=6/sex/group for rhPSMA-7.3 and n=3/sex for vehicle
Deviation from study protocol affecting interpretation of results	No

Source: Reviewer's analysis
Abbreviations: HD, high dose; IV, intravenous; LD, low dose; MD, mid dose; rhPSMA-7.3, radiohybrid prostate-specific membrane antigen-7.3

Table 7. Observations and Results: Changes From Control, Study No. 8391451

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	No significant test article-related findings.
Body weights	No test article-related effects on body weights or body weight gains.
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
Hematology	No toxicology significant test article-related findings.
Clinical chemistry	No toxicology significant test article-related findings.
Urinalysis	No toxicology significant test article-related findings.
Gross pathology	No test article-related macroscopic findings.
Organ weights	Decreased thyroid/parathyroid weight (unadjusted, body weight, and brain weight adjusted) for HD interim sacrifice animals and MD and HD terminal sacrifice males (HD only in females). Findings were not considered to be toxicologically relevant due to the absence of corresponding macroscopic or microscopic changes.
Histopathology Adequate battery: Yes	No test article-related findings.
Other evaluations	No other evaluations were reported.

Source: Reviewer's analysis
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

General Toxicology; Additional Studies

There are no additional studies to be included.

Qualification of (b) (4) an Impurity in Flotufolastat F 18

The Applicant conducted a toxicity risk assessment for an unqualified impurity, (b) (4) in flotufolastat at a level of not more than (b) (4) µg per dose (and up to a maximum of (b) (4) doses per year). The assessment was based on ICH M7(R1) for genotoxic and carcinogenic potential of (b) (4) an impurity and endogenous levels in humans. For mutagenic impurities, the threshold of toxicological concern was set to <120 µg per day for single or infrequent dosing which would be (b) (4)-fold higher than the Applicant's specification limit for (b) (4) impurity. The Applicant also cited endogenous levels (b) (4) at approximately (b) (4) µg (based on a mean blood concentration of 0.1 mg/L and mean human blood volume of 4.5L) which would be over (b) (4)-fold greater than the proposed specification limit for (b) (4) impurity. Therefore, the Applicant is relying on available nonclinical data and regulatory guidance to support the qualification of (b) (4) an impurity presence (< (b) (4) µg per dose) in flotufolastat F 18.

The presence (b) (4) at up to (b) (4) µg per dose is acceptable based on ICH Q3A/B and M7(R1) when considering the frequency of administration, intended population, and endogenous levels in humans.

5.5.3. Genetic Toxicology

Genetic toxicology studies of flotufolastat were not conducted and are not required for microdose radiopharmaceuticals based on the current CDER guidance.

Other Genetic Toxicity Studies

Not applicable.

5.5.4. Carcinogenicity

Carcinogenicity studies are not required for microdose radiopharmaceuticals based on the current CDER guidance.

5.5.5. Reproductive and Developmental Toxicology

The Applicant requested to omit developmental and reproductive toxicity (DART) studies of flotufolastat. The Agency concluded that this request was justified because flotufolastat F 18 is a radiopharmaceutical diagnostic drug that will be administered as a single sub-pharmacologic dose (NMT 100 µg), and the inherent radiation risk to the fetus from radiopharmaceuticals in general is adequately described in the labeling.

The waiver request was granted based on the proposed single-use indication, mass dose, and intended clinical population.

5.5.6. Other Toxicology Studies

No additional toxicology studies of flotufolastat were conducted.

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant seeks approval of Posluma (flotufolastat F 18, a.k.a., radiohybrid prostate-specific membrane antigen (PSMA)-7.3 F 18 (rhPSMA-7.3 F 18)) is a radioactive diagnostic agent indicated for PET imaging of PSMA-positive lesions in men with prostate cancer.

The proposed dose is 296 MBq (8 mCi) as a bolus intravenous injection. Imaging is initiated at approximately 60 minutes after administration. The selection of the dose for flotufolastat F 18 was based on two retrospective chart reviews of patients who received rhPSMA-7 F 18 (Study BED-PSMA-402 and Study BED-PSMA-403).

The primary data to support the Clinical Pharmacology components (biodistribution/dosimetry, pharmacokinetics, plasma metabolic stability, etc.) of the NDA are from Study BED-PSMA-101. Supportive data for the biodistribution of flotufolastat F 18 in patients with prostate cancer are provided from two retrospective chart reviews of patients who received rhPSMA-7 F 18 (Study BED-PSMA-402 and Study BED-PSMA-403).

The biodistribution showed the three organs with the highest mean initial amount of radioactivity one minute after administration were the liver (15.8% of injected radioactivity), the heart content (blood; 7.4% of injected radioactivity), and the kidneys (3.2% of injected radioactivity). In prostate cancer patients, a relatively high amount of radioactivity in the urinary bladder was seen which may obscure visualization of disease in the pelvic region.

The calculated effective dose (ED) for men was 0.0138 mSv/MBq with a 1-hour voiding interval and 0.0141 mSv/MBq with a 3.5-hour voiding interval. The most critical organs (i.e., those with the highest mean absorbed dose per unit of radioactivity administered) were the adrenal glands (0.1835 mGy/MBq), the kidneys (0.1722 mGy/MBq) and the submandibular glands (0.1479 mGy/MBq). The effective radiation dose associated with 296 MBq (8 mCi) of injected activity of Posluma is approximately 4.2 mSv in an adult.

Neither mild nor moderate renal impairment affected the performance of flotufolastat F 18.

Patient-level positive predictive value (PPV) and correct detection rate (CDR) for BCR patients with no prior ADT was 63.2 and 55.3%, respectively whereas, patient-level PPV and CDR for patients with prior ADT was 71.9 and 64.1%, respectively. Thus, in available data, patient-level PPV and CDR are numerically higher for BCR patients with prior ADT as compared to patients with no ADT. This implies that treatment with ADTs may be modulating PSMA expression.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Refer to Section 6.3.1.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose in adult patients is 8 mCi (296 MBq) of flotufolastat F 18, delivered as an intravenous (IV) bolus injection, followed by PET imaging.

In Study BED-PSMA-301, a prospective, phase 3, multi-center, single-arm, single dose, diagnostic imaging study designed to evaluate the safety and diagnostic performance of flotufolastat F 18 for the detection of N1 disease in men with unfavorable intermediate-risk, high-risk, or very high-risk prostate cancer prior to initial definitive therapy, patients received an administered activity of 8 mCi (296 MBq) ±20% of flotufolastat F 18, as an IV bolus injection.

In Study BED-PSMA-302, a prospective, phase 3, multi-center, single-arm, single dose study designed to evaluate the safety and diagnostic performance of flotufolastat F 18 in men with BCR of PC based on elevated PSA, patients also received an administered activity of 8 mCi (296 MBq) ±20% of flotufolastat F 18 as an IV bolus injection.

In both of these phase 3 trials, the administered mass dose of flotufolastat was typically less than 100 µg.

Study BED-PSMA 402

Study BED-PSMA-402 uses rhPSMA-7 F 18, a mixture of four enantiomers (7.1, 7.2, 7.3, and 7.4), of which 7.3 (flotufolastat F 18) is the most abundant enantiomer. In vivo biodistribution studies have shown that the metabolic stability appears acceptable for all four enantiomers and that all appear suitable as candidates for PSMA-targeted PET imaging.

A retrospective, non-interventional chart review of data from patients who underwent rhPSMA-7 F 18 PET scans was performed to evaluate the diagnostic performance and safety of rhPSMA-7 F 18. Data sources included hospital records and imaging results, as well as routine clinical follow-up data.

A total of 1189 patients underwent a clinically indicated rhPSMA-7 F 18 PET/CT or PET/MRI scan in the specified time period. Almost 83% of patients (n=985) underwent PET/CT imaging after F 18 rhPSMA-7 F 18 injection, with the remaining 17% (n=204) undergoing PET/MRI imaging after rhPSMA-7 F 18 injection.

Justification of Administered Activity and Time of Imaging in Study BED-PSMA-402

Quality of the images was assessed by the criteria listed in Table 8, with higher numerical ratings indicating poorer image quality.

Table 8. Qualitative Image Assessment

Item	Response
Subjective image quality overall	1 – Good 2 – Moderate 3 – Poor 4 – Non-interpretable
Unspecific blood pool activity	1 – No 2 – Slight (central vessels) 3 – Moderate (also in peripheral vessels)
Background uptake in bone marrow	1 – No 2 – Slight (≤muscle): no focal spots 3 – Moderate (>muscle): no focal spots 4 – Focal spots (probably not related to tumor lesions)
Impact of biodistribution on clinical decision making	Yes No

Source: BED-PSMA-402 study report

The impact of administered activity, uptake time, and selection of the imaging window on subjective image quality was assessed according to the scheme below (Table 9):

Table 9. Administered Activity and Uptake Time Groups

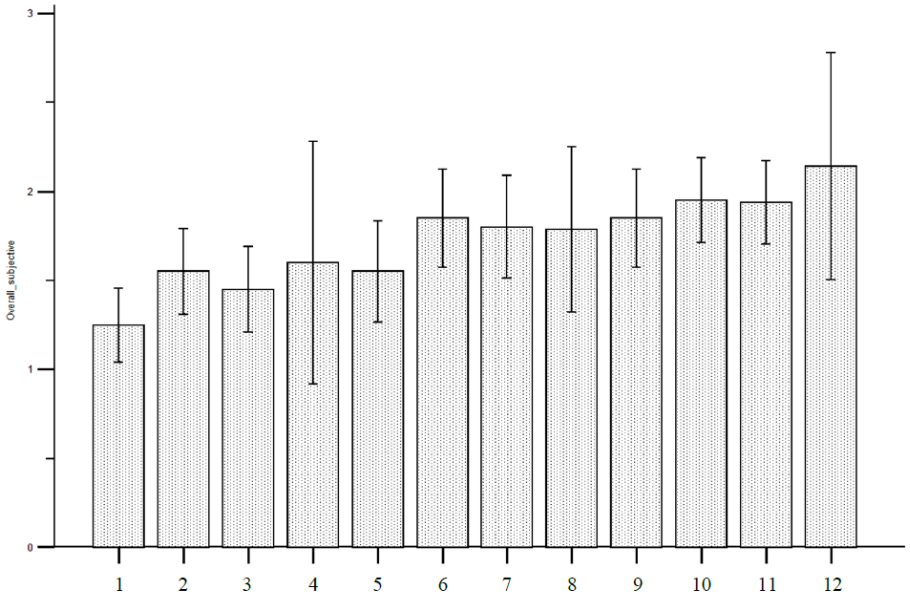
Group	Administered Activity	Time of Imaging	Number of Patients Analyzed
1	222 to 296 MBq (6 to 8 mCi)	50 to 70 minutes	20
2	222 to 296 MBq (6 to 8 mCi)	71 to 90 minutes	20
3	222 to 296 MBq (6 to 8 mCi)	91 to 110 minutes	20
4	222 to 296 MBq (6 to 8 mCi)	≥111 minutes	5
5	297 to 370 MBq (>8 to 10 mCi)	50 to 70 minutes	20
6	297 to 370 MBq (>8 to 10 mCi)	71 to 90 minutes	20
7	297 to 370 MBq (>8 to 10 mCi)	91 to 110 minutes	20
8	297 to 370 MBq (>8 to 10 mCi)	≥111 minutes	14
9	371 to 444 MBq (>10 to 12 mCi)	50 to 70 minutes	20
10	371 to 444 MBq (>10 to 12 mCi)	71 to 90 minutes	20
11	371 to 444 MBq (>10 to 12 mCi)	91 to 110 minutes	16
12	371 to 444 MBq (>10 to 12 mCi)	≥111 minutes	7
TOTAL			**202**
1-4	222 to 296 MBq (6 to 8 mCi)		65
5-8	297 to 370 MBq (>8 to 10 mCi)		74
9-12	371 to 444 MBq (>10 to 12 mCi)		63
1, 5, 9		50 to 70 minutes	60
2, 6, 10		71 to 90 minutes	60
3, 7, 11		91 to 110 minutes	56
4, 8, 12		≥111 minutes	26

MBq=megabecquerel; mCi=millicurie.
Key: Groups 1 to 4: low administered activity group; Groups 5 to 8: moderate administered activity groups; Groups 9 to 12: high administered activity groups.

Source: BED-PSMA-402 study report

There was a trend toward decreased image quality within each group of administered activity as the uptake time increased and within each group of uptake time as administered activity increased, as seen in Figure 2.

Figure 2. Overall Subjective Image Quality by Group



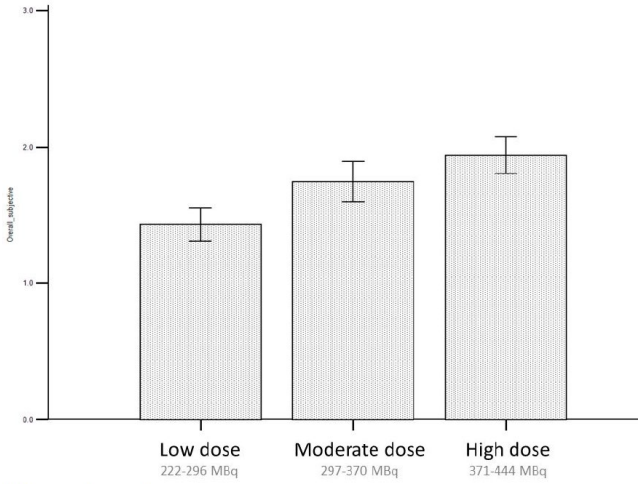
Key: image quality: 1=good; 2=moderate; 3=poor; 4=non-interpretable.

Group					
1:	222 to 296 MBq (6 to 8 mCi); 50 to 70 minutes	2:	222 to 296 MBq (6 to 8 mCi); 71 to 90 minutes	3:	222 to 296 MBq (6 to 8 mCi); 91 to 110 minutes
4:	222 to 296 MBq (6 to 8 mCi); ≥111 minutes	5:	297 to 370 MBq (>8 to 10 mCi); 50 to 70 minutes	6:	297 to 370 MBq (>8 to 10 mCi); 71 to 90 minutes
7:	297 to 370 MBq (>8 to 10 mCi); 91 to 110 minutes	8:	297 to 370 MBq (>8 to 10 mCi); ≥111 minutes	9:	371 to 444 MBq (>10 to 12 mCi); 50 to 70 minutes
10:	371 to 444 MBq (>10 to 12 mCi); 71 to 90 minutes	11:	371 to 444 MBq (>10 to 12 mCi); 91 to 110 minutes	12:	371 to 444 MBq (>10 to 12 mCi); ≥111 minutes

Source: BED-PSMA-402 study report

Pooled analyses also demonstrated trends towards decreased subjective image quality with increasing administered activity (Figure 3) and increasing uptake times (Figure 4).

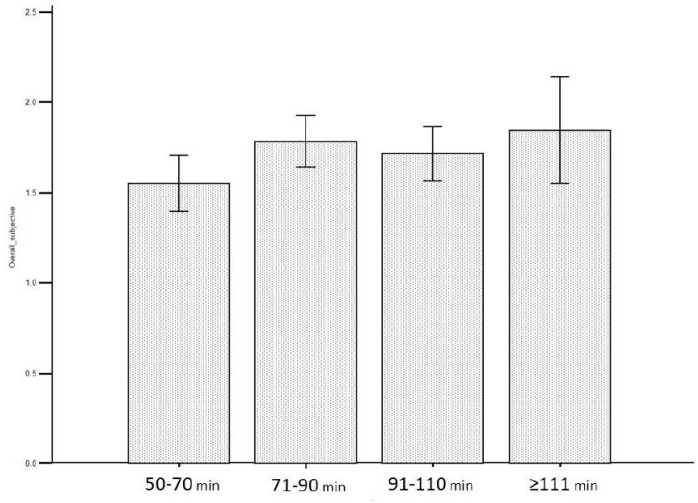
Figure 3. Overall Subjective Image Quality by Administered Activity



MBq=megabecquerel.
Key: image quality: 1.0=good; 2.0=moderate; 3.0=poor; 4.0=non-interpretable.

Source: BED-PSMA-402 study report

Figure 4. Overall Subjective Image Quality by Uptake Time

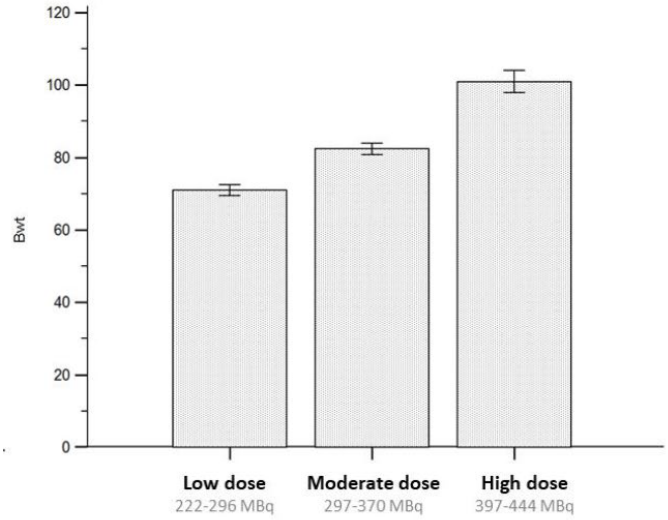


min=minutes.
Key: image quality: 1.0=good; 2.0=moderate; 3.0=poor; 4.0=non-interpretable.

Source: BED-PSMA-402 study report

Subjective image quality within different administered activity groups may have been confounded by bodyweight (Figure 5).

Figure 5. Relationship Between Bodyweight and Administered Activity



Bwt=Bodyweight in kg

Source: BED-PSMA-402 study report

Conclusions

In summary, the qualitative image analysis data demonstrated that increasing uptake time resulted in a trend toward decrease in overall subjective image quality. Based on these results, an imaging time of 50 to 70 minutes is recommended. With regard to administered activity, increasing activity levels resulted in a trend toward decrease in overall image quality, although the data may have been confounded by bodyweight. Additionally, increasing administered activity had no effect on blood pool activity or background uptake in the bone marrow. Considering these points and the desire for recommended administered activity to be applicable across a range of PET scanners, the use of activities >8 to 10 mCi (297 to 370 MBq) is appropriate.

Therapeutic Individualization

None

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

As noted previously, rhPSMA-7 F 18 represents a mixture of four diastereoisomers. It was concluded that any of the four diastereoisomers could likely function as a reasonable PSMA imaging agent compared to other known compounds, with relatively minor differences of note between them. However, rhPSMA-7.3 F 18 (flotufolastat F 18) was considered to be the preferred single diastereoisomer for further development based on in vivo performance, which demonstrated that diastereoisomers, rhPSMA-7.1 F 18 and flotufolastat F 18 had a slightly higher relative accumulation in tumor following administration of the rhPSMA-7 F 18 mixture, with flotufolastat F 18 potentially having a slightly higher overall tumor uptake than rhPSMA-7.1 F 18, with comparably low uptake in other background tissues. Furthermore, flotufolastat F 18 is the most abundant diastereoisomer in the rhPSMA-7 F 18 mixture (~25% to 35% depending on production).

The Applicant conducted a biodistribution and dosimetry, Study BED-PSMA-101. This was a phase 1, open-label, single administration study in healthy volunteers and patients with prostate cancer using flotufolastat F 18. It was performed at a single center and was designed to assess the safety, biodistribution, and internal radiation dosimetry of flotufolastat F 18, as well as to obtain data to optimize the imaging protocol for future studies.

For healthy volunteers, the target administered radioactivity was 225 MBq (±10%). The total radiation effective dose (ED) was not to exceed 10 mSv. The mean administered dose of radioactivity was 220.0 MBq (range: 210 to 228 MBq).

For patients with prostate cancer, the target administered radioactivity was 300 MBq (±10%). Based on the results of the dosimetry analysis of the data obtained from the healthy volunteers, the total ED from administration of flotufolastat F 18 and two CT scans was 10.9 mSv. The mean administered dose of radioactivity was 300.9 MBq (range: 284 to 322 MBq).

Quantitative measurements of F 18 radioactivity in volumes of interest (VOIs) from whole-body healthy volunteer images over target organs were made at several time-points. Time-activity curves were generated and integrated to calculate the cumulated radioactivity in each organ. The OLINDA/EXM software was used to calculate the radiation absorbed doses (ADs) in the target organs using the Medical Internal Radiation Dose (MIRD) schema. This required, as input, the normalized cumulated activities (also known as residence times) for source organs, tissues, and contents. The normalized cumulated radioactivity was the cumulated activity per unit of administered radioactivity. The cumulated activities were then used with the OLINDA/EXM software to calculate the organ ADs to the MIRD target organs in an adult phantom from which the ED was evaluated. A dynamic urinary bladder model was used and the internal radiation dosimetry was calculated for 1-hour and 3.5-hour urinary bladder voiding intervals. The effects of the voiding interval upon the urinary bladder wall dose and the ED were also evaluated.

Biodistribution

The three organs with the highest mean initial amount of radioactivity one minute after injection were liver (15.8% of injected radioactivity; range: 13.9% to 17.0%), heart content (blood; 7.4% of injected radioactivity; range: 6.5% to 9.2%), and kidneys (3.2% of injected radioactivity; range: 2.5% to 3.5%). Also, skeletal muscles (mean initial uptake 24.3% of injected radioactivity; range: 19.2% to 29.3%) and cortical bone (3.5% of injected radioactivity; range: 3.0% to 4.4%) showed high relative uptake values because of their very large organ volumes. Over the whole scanning period, the organs with the highest relative uptake were skeletal muscle, liver, and kidneys.

For imaging of prostate cancer, the relatively high amount of radioactivity in the urinary bladder of healthy volunteers is worth noting. It was clearly increased at the Scan 2 imaging point 7 minutes post-administration and was further increased at later scans although the healthy volunteers urinated both between the first and second and between the second and third scan sessions. At the end of the first scanning session (mean time, 111 minutes post-administration), the mean results from the 6 healthy volunteers indicated that 7.2% (range: 4.4% to 9.0%) of the injected radioactivity was excreted into urine. The mean cumulative proportion of radioactivity in urine was 7.2%, 11.4%, and 14.8% after scanning 90 min, 178 min and 248 min, respectively. Considerable variability in the urinary excretion was noted.

Dosimetry

Biodistribution data from all 6 healthy volunteers were used in the calculation of the ED by using the Cristy and Eckerman adult male phantom. The calculated ED for men was 0.0138 mSv/MBq with a 1-hour voiding interval and 0.0141 mSv/MBq with a 3.5-hour voiding interval. The most critical organs (i.e., those with the highest mean absorbed dose per unit administered radioactivity) were the adrenal glands (0.1835 mGy/MBq), the kidneys (0.1722 mGy/MBq), and submandibular glands (0.1479 mGy/MBq).

Lesion Kinetics

Tissue radioactivity concentrations and lesion-to-reference ratios increased at least up to the end of the second scanning session (118 minutes post-injection). The increases were not substantial after the first whole-body scan, and optimal visual detection of primary tumors and/or metastases was achieved at 60 minutes post-injection. Blood radioactivity concentrations decreased rapidly after radiopharmaceutical administration, as flotufolastat F 18 was distributed in the blood pool and in the tissues of the body. Tissue-to-blood ratios generally increased with time, suggesting a significant irreversible uptake component.

Lesion Detectability

Whole-body flotufolastat F 18 PET/CT scans at 60 minutes post-injection identified all prostate cancer lesions defined according to standard of care imaging, and in five patients with metastatic disease, new lesions classified as prostate cancer were detected.

IHC and Gleason Score

PSMA Immunohistochemistry (IHC) staining of representative macro blocks of prostate specimens from patients was performed. Intra-focal heterogeneity was evident in the majority of tumor lesions. Only one lesion showed an even PSMA IHC staining distribution throughout the lesion. None of the lesions was fully negative for PSMA staining. There was a clear trend for higher grade tumors to show more intense PSMA staining. Gleason 4 and 5 patterns showed strong staining, while the Gleason 3 pattern was typically weak or negative. In all lesions, the PSMA staining pattern was in the cytoplasmic and at the apical (luminal) plasma membrane. In low/moderate expressing carcinoma cells (score 1+/2+), the PSMA staining was more easily visible at the apical plasma membrane similar to normal positive glands. Heterogeneous PSMA expression in normal prostate glands was frequently observed and intraluminal macrophages typically stained strongly, possibly because they had phagocytized PSMA from detached epithelial cells.

Supportive real-world-data are provided from published literature and from two retrospective chart reviews (Study BED-PSMA-402 and Study BED-PSMA-403) performed by the Technical University of Munich (TUM).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy of flotufolastat F 18 is not based directly on pharmacokinetics (exposure response/ imaging). As such, clinical pharmacology information provides limited or no supportive evidence of effectiveness.

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

The proposed dosing appears appropriate for imaging of PSMA-positive prostate cancer in the indicated populations.

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

No alternative dosing regimen is required for subpopulations based on intrinsic factors.

Is there an effect of body weight of the clinical performance of flotufolastat F 18?

The effect of body weight on image quality/efficacy of flotufolastat F 18 was evaluated. Patients in Studies BED-PSMA-301 and BED-PSMA-302 were administered an activity of 296 MBq (8mCi) ±20%. The Applicant normalized the administered activity to bodyweight in the studies. The median administered activity per kilogram was 3.477 MBq/kg for Study BED-PSMA-301 and 3.453 MBq/kg for Study BED-PSMA-302. For BED-PSMA-301, diagnostic performance for N1

disease in Efficacy Analysis Population (EAP) patients with administered activity ≤ median dose (3.477 MBq/kg) showed a trend toward higher sensitivity for the three readers (36%, 36%, 33%) as compared to patients that received administered activity >3.477 MBq/kg (25%, 22%, 11% for three blinded readers) (Tables 10 and 11). It is not clear if this trend is clinically meaningful.

Table 10. BED-PSMA-301 - Diagnostic Performance for N1 Disease for Patients (EAP) with Administered Activity ≤ Median Dose (3.477 MBq/kg)

Parameter	Blinded PET Reader 1 (N=148)	Blinded PET Reader 2 (N=148)	Blinded PET Reader 3 (N=148)
True Positive	12 (8.1%)	11 (7.4%)	12 (8.1%)
False Positive	11 (7.4%)	7 (4.7%)	5 (3.4%)
False Negative	21 (14.2%)	22 (14.9%)	21 (14.2%)
True Negative	104 (70.3%)	108 (73.0%)	110 (74.3%)
Sensitivity (%)	12/33 (36.4%)	11/33 (33.3%)	12/33 (36.4%)
(95% CI)	[20.4% - 54.9%]	[18.0% - 51.8%]	[20.4% - 54.9%]
Specificity (%)	104/115 (90.4%)	108/115 (93.9%)	110/115 (95.7%)
(95% CI)	[83.5% - 95.1%]	[87.9% - 97.5%]	[90.1% - 98.6%]
PPV	12/23 (52.2%)	11/18 (61.1%)	12/17 (70.6%)
(95% CI)	[30.6% - 73.2%]	[35.7% - 82.7%]	[44.0% - 89.7%]
NPV	104/125 (83.2%)	108/130 (83.1%)	110/131 (84.0%)
(95% CI)	[75.5% - 89.3%]	[75.5% - 89.1%]	[76.5% - 89.8%]
Histopathology positive	33/148 (22.3%)	33/148 (22.3%)	33/148 (22.3%)
(95% CI)	[15.9% - 29.9%]	[15.9% - 29.9%]	[15.9% - 29.9%]

Source: Response to clinical pharmacology information request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Table 11. BED-PSMA-301 - Diagnostic Performance for N1 Disease for Patients (EAP) with Administered Activity > Median Dose (3.477 MBq/kg)

Parameter	Blinded PET Reader 1 (N=147)	Blinded PET Reader 2 (N=147)	Blinded PET Reader 3 (N=147)
True Positive	9 (6.1%)	8 (5.4%)	4 (2.7%)
False Positive	5 (3.4%)	7 (4.8%)	2 (1.4%)
False Negative	27 (18.4%)	28 (19.0%)	32 (21.8%)
True Negative	106 (72.1%)	104 (70.7%)	109 (74.1%)
Sensitivity (%)	9/36 (25.0%)	8/36 (22.2%)	4/36 (11.1%)
(95% CI)	[12.1% - 42.2%]	[10.1% - 39.2%]	[3.1% - 26.1%]
Specificity (%)	106/111 (95.5%)	104/111 (93.7%)	109/111 (98.2%)
(95% CI)	[89.8% - 98.5%]	[87.4% - 97.4%]	[93.6% - 99.8%]
PPV	9/14 (64.3%)	8/15 (53.3%)	4/6 (66.7%)
(95% CI)	[35.1% - 87.2%]	[26.6% - 78.7%]	[22.3% - 95.7%]
NPV	106/133 (79.7%)	104/132 (78.8%)	109/141 (77.3%)
(95% CI)	[71.9% - 86.2%]	[70.8% - 85.4%]	[69.5% - 83.9%]
Histopathology positive	36/147 (24.5%)	36/147 (24.5%)	36/147 (24.5%)
(95% CI)	[17.8% - 32.3%]	[17.8% - 32.3%]	[17.8% - 32.3%]

Source: Response to clinical pharmacology information request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

In BED-PSMA-301, diagnostic performance on M1 disease for patients with administered activity ≤ median dose (3.477 MBq/kg) and greater than 3.477 MBq/kg were similar at patient-level and region-level (data not shown).

In BED-PSMA-302, diagnostic performance for patients with administered activity ≤ median dose (3.453 MBq/kg) and >3.453 MBq/kg were similar at patient-level and region-level (data not shown).

In total, analyses using a median threshold did not demonstrate a convincing effect of body weight on performance of flotufolastat F 18.

What is the effect of renal impairment of the efficacy of flotufolastat F 18?

The primary and key secondary endpoint data for BED-PSMA-301 are presented below based on renal function. The definitions used for renal impairment are:

- eGFR ≥90 mL/min/1.73m^2 = Normal
- eGFR 60 to <90 mL/min/1.73m^2 = Mild impairment
- eGFR 30 to <60 mL/min/1.73m^2 = Moderate impairment
- eGFR <30 mL/min/1.73m^2 = Severe impairment

Tables 12 to 14 show that there was no definite effect of renal function on the performance (sensitivity and efficacy) of the drug. There were only 11 patients with moderate renal impairment and only 3 patients with severe renal impairment.

Table 12. BED-PSMA-301 - Diagnostic Performance for N1 Disease for Patients (EAP) with eGFR ≥90

Parameter	Blinded PET Reader 1 (N=112)	Blinded PET Reader 2 (N=112)	Blinded PET Reader 3 (N=112)
True Positive	10 (8.9%)	10 (8.9%)	6 (5.4%)
False Positive	3 (2.7%)	3 (2.7%)	1 (0.9%)
False Negative	23 (20.5%)	23 (20.5%)	27 (24.1%)
True Negative	76 (67.9%)	76 (67.9%)	78 (69.6%)
Sensitivity (%)	10/33 (30.3%)	10/33 (30.3%)	6/33 (18.2%)
(95% CI)	[15.6% - 48.7%]	[15.6% - 48.7%]	[7.0% - 35.5%]
Specificity (%)	76/79 (96.2%)	76/79 (96.2%)	78/79 (98.7%)
(95% CI)	[89.3% - 99.2%]	[89.3% - 99.2%]	[93.1% - 100.0%]
PPV	10/13 (76.9%)	10/13 (76.9%)	6/7 (85.7%)
(95% CI)	[46.2% - 95.0%]	[46.2% - 95.0%]	[42.1% - 99.6%]
NPV	76/99 (76.8%)	76/99 (76.8%)	78/105 (74.3%)
(95% CI)	[67.2% - 84.7%]	[67.2% - 84.7%]	[64.8% - 82.3%]
Histopathology positive	33/112 (29.5%)	33/112 (29.5%)	33/112 (29.5%)
(95% CI)	[21.2% - 38.8%]	[21.2% - 38.8%]	[21.2% - 38.8%]

Source: Response to clinical pharmacology information request

Abbreviations: CI, confidence interval; EAP, efficacy analysis population; eGFR, estimated glomerular filtration rate; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Table 13. BED-PSMA-301 - Diagnostic Performance for N1 Disease for Patients (EAP) for eGFR 60 to <90

Parameter	Blinded PET Reader 1 (N=141)	Blinded PET Reader 2 (N=141)	Blinded PET Reader 3 (N=141)
True Positive	10 (7.1%)	8 (5.7%)	8 (5.7%)
False Positive	12 (8.5%)	9 (6.4%)	5 (3.5%)
False Negative	17 (12.1%)	19 (13.5%)	19 (13.5%)
True Negative	102 (72.3%)	105 (74.5%)	109 (77.3%)
Sensitivity (%)	10/27 (37.0%)	8/27 (29.6%)	8/27 (29.6%)
(95% CI)	[19.4% - 57.6%]	[13.8% - 50.2%]	[13.8% - 50.2%]
Specificity (%)	102/114 (89.5%)	105/114 (92.1%)	109/114 (95.6%)
(95% CI)	[82.3% - 94.4%]	[85.5% - 96.3%]	[90.1% - 98.6%]
PPV	10/22 (45.5%)	8/17 (47.1%)	8/13 (61.5%)
(95% CI)	[24.4% - 67.8%]	[23.0% - 72.2%]	[31.6% - 86.1%]
NPV	102/119 (85.7%)	105/124 (84.7%)	109/128 (85.2%)
(95% CI)	[78.1% - 91.5%]	[77.1% - 90.5%]	[77.8% - 90.8%]
Histopathology positive	27/141 (19.1%)	27/141 (19.1%)	27/141 (19.1%)
(95% CI)	[13.0% - 26.6%]	[13.0% - 26.6%]	[13.0% - 26.6%]

Source: Response to clinical pharmacology information request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; eGFR, estimated glomerular filtration rate; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Table 14. BED-PSMA-301 - Diagnostic Performance for N1 Disease for Patients (EAP) with eGFR 30 to <60

Parameter	Blinded PET Reader 1 (N=11)	Blinded PET Reader 2 (N=11)	Blinded PET Reader 3 (N=11)
True Positive	1 (9.1%)	1 (9.1%)	1 (9.1%)
False Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)
False Negative	2 (18.2%)	2 (18.2%)	2 (18.2%)
True Negative	8 (72.7%)	8 (72.7%)	8 (72.7%)
Sensitivity (%)	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)
(95% CI)	[0.8% - 90.6%]	[0.8% - 90.6%]	[0.8% - 90.6%]
Specificity (%)	8/8 (100.0%)	8/8 (100.0%)	8/8 (100.0%)
(95% CI)	[63.1% - 100.0%]	[63.1% - 100.0%]	[63.1% - 100.0%]
PPV	1/1	1/1	1/1
(95% CI)	[2.5% - 100.0%]	[2.5% - 100.0%]	[2.5% - 100.0%]
NPV	8/10 (80.0%)	8/10 (80.0%)	8/10 (80.0%)
(95% CI)	[44.4% - 97.5%]	[44.4% - 97.5%]	[44.4% - 97.5%]
Histopathology positive	3/11 (27.3%)	3/11 (27.3%)	3/11 (27.3%)
(95% CI)	[6.0% - 61.0%]	[6.0% - 61.0%]	[6.0% - 61.0%]

Source: Response to clinical pharmacology information request

Abbreviations: CI, confidence interval; EAP, efficacy analysis population; eGFR, estimated glomerular filtration rate; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

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

The effect of androgen deprivation therapies (ADT) on image quality and efficacy of flotufolastat F 18 was conducted for both BED-PSMA-301 and BED-PSMA-302 studies.

For study BED-PSMA-301, patients were excluded who were currently receiving, or with a prior history of ADT, defined as surgical orchidectomy, luteinizing hormone-releasing hormone (LHRH) agonist alone (continuous or intermittent), LHRH antagonist alone (continuous or intermittent), and first generation or second-generation anti-androgen alone or in combination with an LHRH agonist/antagonist.

The BED-PSMA-302 protocol inclusion criteria allowed patients to have had prior treatment with ADT, as long as the ADT had been discontinued at least 16 weeks prior to screening.

In BED-PSMA-302, overall region-level PPV was 58.9% for patients with no prior ADT and 63.2% for patients with prior ADT (Tables 15 and 16). Patient-level PPV and CDR for patients with no prior ADT were 63.3 and 55.3%, respectively, whereas patient-level PPV and CDR for patients with prior ADT were 71.9 and 64.1%, respectively (Tables 15 and 16). These trends suggest that treatment with ADT may be modulating PSMA expression. The clinical significance of these results is not clear.

Table 15. BED-PSMA-302 – Region-Level PPV, Patient-Level PPV, and CDR for Patients with No Prior ADT

Region level PPV	Statistic	Blinded PET Reader 1 (N=302)	Blinded PET Reader 2 (N=302)	Blinded PET Reader 3 (N=302)	Majority of Blinded PET Readers (N=302)
Prostate/Prostate Bed	True Positive (=PPV)	51/219 (23.3%)	39/84 (46.4%)	42/128 (32.8%)	49/126 (38.9%)
	False Positive	168/219 (76.7%)	45/84 (53.6%)	86/128 (67.2%)	77/126 (61.1%)
Pelvic Lymph Nodes	True Positive (=PPV)	67/102 (65.7%)	59/91 (64.8%)	68/115 (59.1%)	67/96 (69.8%)
	False Positive	35/102 (34.3%)	32/91 (35.2%)	47/115 (40.9%)	29/96 (30.2%)
Other sites	True Positive (=PPV)	80/115 (69.6%)	86/134 (64.2%)	71/111 (64.0%)	85/119 (71.4%)
	False Positive	35/115 (30.4%)	48/134 (35.8%)	40/111 (36.0%)	34/119 (28.6%)
Overall (prostate/prostate bed, pelvic lymph nodes, other sites)	True Positive (=PPV)	198/436 (45.4%)	184/309 (59.5%)	181/354 (51.1%)	201/341 (58.9%)
	False Positive	238/436 (54.6%)	125/309 (40.5%)	173/354 (48.9%)	140/341 (41.1%)
All 3 regions	95% CI for PPV	[40.7% - 50.1%]	[54.1% - 65.0%]	[45.9% - 56.3%]	[53.7% - 64.2%]

Patient level PPV & CDR	Blinded PET Reader 1 (N=302)	Blinded PET Reader 2 (N=302)	Blinded PET Reader 3 (N=302)	Majority of Blinded PET Readers (N=302)
True Positive	159/296 (53.7%)	150/211 (71.1%)	151/262 (57.6%)	167/264 (63.3%)
False Positive	137/296 (46.3%)	61/211 (28.9%)	111/262 (42.4%)	97/264 (36.7%)
PPV	159/296 (53.7%)	150/211 (71.1%)	151/262 (57.6%)	167/264 (63.3%)
95% CI	[47.9% - 59.5%]	[64.5% - 77.1%]	[51.4% - 63.7%]	[57.1% - 69.1%]
CDR	159/302 (52.6%)	150/302 (49.7%)	151/302 (50.0%)	167/302 (55.3%)
95% CI	[46.9% - 58.4%]	[43.9% - 55.5%]	[44.2% - 55.8%]	[49.5% - 61.0%]

Source: Response to clinical pharmacology information request
Abbreviations: ADT, androgen deprivation therapy; CDR, correct detection rate; CI, confidence interval; PET, positron emission tomography; PPV, positive predictive value

Table 16. BED-PSMA-302 – Region-Level PPV, Patient-Level PPV, and CDR for Patients with Any Prior ADT

Region level PPV	Statistic	Blinded PET Reader 1 (N=64)	Blinded PET Reader 2 (N=64)	Blinded PET Reader 3 (N=64)	Majority of Blinded PET Readers (N=64)
Prostate/Prostate Bed	True Positive (=PPV)	10/36 (27.8%)	9/16 (56.3%)	8/19 (42.1%)	8/19 (42.1%)
	False Positive	26/36 (72.2%)	7/16 (43.8%)	11/19 (57.9%)	11/19 (57.9%)
Pelvic Lymph Nodes	True Positive (=PPV)	12/25 (48.0%)	12/20 (60.0%)	14/23 (60.9%)	13/21 (61.9%)
	False Positive	13/25 (52.0%)	8/20 (40.0%)	9/23 (39.1%)	8/21 (38.1%)
Other sites	True Positive (=PPV)	27/38 (71.1%)	26/38 (68.4%)	23/34 (67.6%)	27/36 (75.0%)
	False Positive	11/38 (28.9%)	12/38 (31.6%)	11/34 (32.4%)	9/36 (25.0%)
Overall (prostate/ prostate bed, pelvic lymph nodes, other sites)	True Positive (=PPV)	49/99 (49.5%)	47/74 (63.5%)	45/76 (59.2%)	48/76 (63.2%)
	False Positive	50/99 (50.5%)	27/74 (36.5%)	31/76 (40.8%)	28/76 (36.8%)
All 3 regions	95% CI for PPV	[39.6% - 59.3%]	[52.5% - 74.5%]	[48.2% - 70.3%]	[52.3% - 74.0%]

Patient level PPV & CDR	Blinded PET Reader 1 (N=64)	Blinded PET Reader 2 (N=64)	Blinded PET Reader 3 (N=64)	Majority of Blinded PET Readers (N=64)
True Positive	39/61 (63.9%)	38/52 (73.1%)	38/59 (64.4%)	41/57 (71.9%)
False Positive	22/61 (36.1%)	14/52 (26.9%)	21/59 (35.6%)	16/57 (28.1%)
PPV	39/61 (63.9%)	38/52 (73.1%)	38/59 (64.4%)	41/57 (71.9%)
95% CI	[50.6% - 75.8%]	[59.0% - 84.4%]	[50.9% - 76.4%]	[58.5% - 83.0%]
CDR	39/64 (60.9%)	38/64 (59.4%)	38/64 (59.4%)	41/64 (64.1%)
95% CI	[47.9% - 72.9%]	[46.4% - 71.5%]	[46.4% - 71.5%]	[51.1% - 75.7%]

Source: Response to clinical pharmacology information request
Abbreviations: ADT, androgen deprivation therapy; CDR, correct detection rate; CI, confidence interval; PET, positron emission tomography; PPV, positive predictive value

Has an adequate scientific bridge been established between flotufolastat F 18 vs F 18 rhPSMA-7?

Yes. Comparability of the diastereoisomer mixture (rhPSMA-7 F 18) and rhPSMA-7.3 F 18 (flotufolastat F 18) was demonstrated.

The retrospective chart review of data in Study BED-PSMA-402 to evaluate the impact of administered activity and uptake time on subjective image quality was performed with rhPSMA-7 F 18 PET scans. In contrast, the phase 3 studies, BED-PSMA-301 and BED-PSMA-302, and biodistribution and dosimetry study BED-PSMA-101 used rhPSMA-7.3 F 18 (flotufolastat F 18).

In study BED-PSMA-403, quantitative biodistribution (SUV) was compared between rhPSMA-7 F 18 and flotufolastat F 18. Briefly, 33 flotufolastat F 18 PET/CT scans and 47 rhPSMA-7 F 18 PET/CT scans were analyzed. The mean age (71 vs. 70 years), injected activity (345 vs. 324 MBq), and acquisition time (76 vs. 84 minutes) were similar. The results indicated that the quantitative organ biodistribution between flotufolastat F 18 and rhPSMA-7 F 18 were similar (Table 17). Although radiotracer retention in the urinary bladder was different, the retention was relatively low.

Table 17. BED-PSMA-403 - Biodistribution (SUV_{mean}) of rhPSMA-7.3 F 18 (flotufolastat F 18) versus rhPSMA-7 F 18 by Organ

Organ	Mean±SD		P-value
	rhPSMA-7 (^{18}F)	rhPSMA-7.3 (^{18}F)	
Absolute SUV_{mean}			
Background	0.63±0.17	0.66±0.13	0.065[a]
Parotid gland	16.94±5.98	16.19± 4.42	0.549[b]
Submandibular gland	19.63±5.32	19.86±5.45	0.854[b]
Blood pool	1.99±2.26	1.85±0.32	0.028[a]
Lungs	0.68±0.32	0.68±0.19	0.511[a]
Liver	6.98±2.31	7.29±2.24	0.556[b]
Spleen	9.14±3.24	8.44±3.23	0.338[a]
Kidney	32.38± 9.33	35.74±9.72	0.195[a]
Pancreas	2.54±0.87	2.84±0.98	0.177[a]
Duodenum	10.94±4.22	10.96±4.66	0.981[b]
Bone	1.10±0.33	1.34±0.40	**0.005[b]**
Bladder	6.31±12.94	2.00±0.78	**0.001[a]**
Tumor	20.03±20.23	32.54±42.71	0.071[a]

Source: Table A2, Appendix 1, Module 2.
Bold: p-values are statistically significant. [a]Mann-Whitney U Test; [b]Independent Student T-test
Abbreviations: rhPSMA, radiohybrid prostate-specific membrane antigen; SD, standard deviation; SUV, standardized uptake value

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 18. Listing of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Primary Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
BED-PSMA-301 (LIGHTHOUSE)	NCT04186819	Prospective, single-arm, open-label	Single 8 mCi ±20% IV injection of flotufolastat F 18	Patient-level sensitivity and specificity for pelvic lymph node metastases by histopathology reference	356	Patients with unfavorable intermediate, high, or very high-risk PC scheduled for RP and PLND	34 sites (31 recruited patients) 4 countries (USA, Finland, Germany, Netherlands) 29 USA, 2 Germany, 1 Finland, 2 Netherlands
BED-PSMA-302 (SPOTLIGHT)	NCT04186845	Prospective, single-arm, open-label	Single 8 mCi ±20% IV injection of flotufolastat F 18	Patient-level CDR and region-level PPV by composite reference standard	391	Patients with BCR of PC per AUA or Phoenix criteria who were eligible for salvage therapy	28 sites (27 recruited patients) 3 countries (USA, Finland, Netherlands) 25 USA, 1 Finland, 2 Netherlands

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Primary Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
BED-PSMA-101	NCT03995888	Prospective, single-arm, open-label	Single 6 mCi +/- 10% IV injection of flotufolastat F 18 for healthy volunteers Single 8 mCi +/- 10% IV injection of flotufolastat F 18 for PC patients	AEs, clinical laboratory tests, vital signs, 12-lead EKG, PE	6 healthy volunteers (3 male and 3 female) 9 patients with PC (3 scheduled for prostatectomy, 3 with hormone-sensitive metastatic PC, 3 with castrate-resistant metastatic PC)	Healthy male and female volunteers Patients with unfavorable intermediate-risk, high-risk PC scheduled for prostatectomy, hormone-sensitive metastatic PC, or castrate-resistant metastatic PC	1 center in Finland

Source: FDA Clinical Reviewer
Abbreviations: AE, adverse event; AUA, American Urological Association; BCR, biochemical recurrence; CDR, correct detection rate; CT, computed tomography; EKG, electrocardiogram; IV, intravenous; MRI, magnetic resonance imaging; NPV, negative predictive value; PC, prostate cancer; PE, physical examination; PET, positron emission tomography; PLND, pelvic lymph node dissection; PPV, positive predictive value; PSA, prostate-specific antigen; rhPSMA, radiohybrid prostate-specific membrane antigen; RP, radical prostatectomy; VDR, verified detection rate

7.2. Review Strategy

Primary evidence of effectiveness and safety for flotufolastat F 18 for imaging of PC was provided in two prospective trials, BED-PSMA-301 (LIGHTHOUSE) and BED-PSMA-302 (SPOTLIGHT). These trials were conducted in two distinct populations, patients with a new diagnosis of PC (unfavorable intermediate-risk, high-risk, or very high-risk) who were candidates for definitive treatment with prostatectomy and patients with BCR of PC after curative intent treatment. Additional safety data was provided by a BED-PSMA-101, which included healthy volunteers as well as patients with PC at various stages of the disease.

Two retrospective chart review studies, BED-PSMA-402 and BED-PSMA-403, were submitted to provide supportive efficacy and safety data. Since BED-PSMA-402 used ^{18}F-rhPSMA-7, which is a mix of diastereoisomers that includes flotufolastat F 18, the data from this trial are not directly pertinent to evaluation of flotufolastat F 18 and so were not assessed in detail during the review. BED-PSMA-403 was also not examined in depth due to the retrospective nature of the study and the fact that the chart review included a mixed PC population, including a significant number of patients with metastatic castrate-resistant PC, that is very different from the populations studied in BED-PSMA-301 or BED-PSMA-302. Only a small number of patients were imaged before definitive treatment in this study, and an even smaller percentage of this subgroup had histopathology for SoT determination, which did not allow for any conclusions to be made regarding the efficacy of flotufolastat F 18 in this population. For patients with BCR, no SoT was used to validate PET-positive lesions, and so there was no verified endpoint for this patient population. Therefore, these studies are not discussed in the efficacy review in Section 8, and BED-PSMA-403 is mentioned only briefly as supportive safety information.

Unless otherwise specified, all analyses of the data from these trials reported in Section 8.1 Review of Relevant Individual Trials Used to Support Efficacy and 8.2 Review of Safety of the review were performed by the Applicant with assessment and commentary of the Clinical Reviewer. Additional analyses to supplement those performed by the Applicant were performed by the Clinical Reviewer or by the Statistics team as notated in the review.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BED-PSMA-301 (LIGHTHOUSE)

Trial Design

BED-PSMA-301 (LIGHTHOUSE) was a prospective, single-arm, open-label trial to assess the sensitivity and specificity of flotufolastat F 18 positron emission tomography (PET) in detecting pelvic lymph node metastasis compared to histopathology from RP and PLND. The study was performed in the United States, Finland, Germany, and the Netherlands. Results from patients

enrolled in Finland, Germany, and the Netherlands should be applicable to the United States population.

This trial enrolled adult males with newly diagnosed, untreated, biopsy-proven unfavorable intermediate-risk, high-risk, or very high-risk PC by NCCN Guidelines v.1.2020 criteria who were planned for RP and PLND. Patients with current or prior history of androgen deprivation therapy (ADT) were excluded. Patients were to have baseline conventional imaging consisting of a CT or MRI of the abdomen/pelvis, chest CT, or bone scan 60 days prior to screening or at least 24 hours before administration of flotufolastat F 18 for the investigational PET imaging.

After enrollment, each patient was administered 8 mCi +/- 20% of flotufolastat F 18 intravenously. As discussed in Section 6 of this review, the dose was selected based on BED-PSMA-101 dosimetry data and research at the Technical University of Munich that identified the range of administered activity that would result in highest overall image quality. PET/CT images of the skull base through mid-thigh were obtained 50-70 minutes after injection of flotufolastat F 18.

The flotufolastat F 18 PET images were reviewed by one local reader at the study site to determine if N1 or M1 disease was present and to guide further diagnostic testing or management. Patients with M1 disease detected by the local read of the flotufolastat F 18 PET images were to undergo a confirmatory biopsy (or surgery if part of the patient's management) or confirmatory imaging. Confirmatory imaging for assessment of M1 disease could include a CT, MRI, bone scan, ultrasound, ^{18}F-fluciclovine PET, or ^{18}F-sodium fluoride PET and was reviewed centrally by three central readers who had access to all available imaging but were blinded to local site interpretation of these images. The three central readers also had access to a brief summary of clinical information and reached a consensus on PET-positive lesions. Those patients with confirmed M1 disease could have their treatment plan modified as determined by the responsible physician.

Patients proceeded to the planned standard-of-care RP and PLND within 60 days of flotufolastat F 18 injection. RP and PLND could be performed open, robotically, or laparoscopically by a qualified surgeon. PLND included, at minimum, resection of lymphatic tissue for histological analysis from the hypogastric (internal iliac), external iliac, and obturator lymph node regions. Extended lymph node dissections to include regions such as the pre-sacral, common iliac, and peri-rectal nodal groups could be performed as indicated. Resected lymph node tissue was labeled to match the anatomic site of origin with designation of laterality. The lymph node specimens were processed and analyzed by a pathologist per standard of care for the presence of PC. Patients could also undergo external beam radiation (EBRT) if preferred over surgery by the patient and physician.

The flotufolastat F 18 PET images were also sent to a contract research organization, (b) (4) (b) (4) to be read by three independent central readers who were blinded to conventional imaging results. This central blinded image evaluation (BIE) was performed for assessment of the study endpoints. All local and central readers were trained in the interpretation of flotufolastat F 18 PET scans.

Vital signs were performed at screening and pre and post flotufolastat F 18 injection. A 12-lead EKG was performed before flotufolastat F 18 and at a safety follow-up visit up to 5 days after flotufolastat F 18 injection, and a focused physical exam was performed at the screening visit and safety follow-up visit. Adverse events (AEs) were recorded at each visit.

Study Endpoints

The co-primary endpoints were patient-level sensitivity and patient-level specificity of flotufolastat F 18 PET/CT for detection of pelvic lymph node PC metastases against a histopathology reference standard derived from tissue removed during PLND. These endpoints were discussed and agreed upon in a meeting between the FDA and the Applicant on 6/19/2019.

Localized PC is usually treated with observation, radiation, or surgery, depending on risk factors for aggressiveness. Prostatectomy is usually not performed in patients with disease that has spread outside the prostate gland, and appropriateness of radiation treatment often depends on the location and extent of disease outside the prostate gland. Decisions on management therefore depend on accurately detecting and localizing sites of extraprostatic disease. Unfortunately, approved imaging modalities that are available have limited sensitivity and specificity for detecting pelvic lymph node and distant metastases. Therefore, there is a need for agents that can correctly image these lesions.

PC typically spreads to pelvic lymph nodes first before metastasizing to more distant sites outside of the pelvis, and assessment of pelvic lymph nodes is usually performed via PLND at time of prostatectomy. For these reasons, assessing the performance of flotufolastat F 18 PET for detection of pelvic lymph node metastases as an endpoint is both pragmatic and clinically pertinent.

During the central PET reads, a positive or negative designation was made for the prostate gland, pelvic lymph nodes, lymph nodes outside the pelvis, soft tissue/parenchyma, and bones. A positive lesion was defined as “uptake greater than background and being consistent with prostate cancer,” per the BED-PSMA-301 (b) (4) Independent Review Training Manual. Up to three representative positive bone lesions per subregion were annotated (subregions = skull, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, sacral vertebrae, pelvic bones, chest bones, and appendicular bones). True positivity or true negativity was first defined in the hemipelvis region. At least one flotufolastat F 18 PET positive lymph node and one positive lymph node as established by histopathology on the same side of the pelvis on the left or right was labeled as a true positive (TP) at the region-level and at the patient-level. If there was at least one PET-positive lymph node in the hemipelvis region, but no pathology-positive lymph node, then that was considered a false positive (FP) region. No PET-positive lymph node in a hemipelvis region with a pathology-positive lymph node was considered a false negative (FN) region, and no PET-positive lymph node in a hemipelvis region without a pathology-positive lymph node was considered a true negative (TN) region. In patients without a TP region, patient-level classification was determined by the following table.

Table 19. Patient-Level Categorization in Patients With No True Positive Regions

Patient-level Categorization	At Least One True Negative (TN) Region	At Least One False Negative (FN) Region	At Least One False Positive (FP) Region
True Negative (TN)	Yes	No	No
False Negative (FN)	Yes	Yes	No
False Negative (FN)	No	Yes	No
False Positive (FP)	Yes	No	Yes
False Positive (FP)	No	No	Yes
False Negative (FN) for Primary Analysis; False Positive (FP) for Secondary Analysis[a]	No	Yes	Yes

Source: BED-PSMA-301 Clinical Study Report (p.45)

Therefore, patients with both a FN region and a FP region were classified overall as FN at the patient-level for the primary analysis and as FP for the secondary analysis, as shown in the table below.

Table 20. Patient Level Classification Based on Region-Level Categorization

Histopathology	PET Patient-level Classification			
	True Positive (TP)	False Negative (FN)	False Positive (FP)	True Negative (TN)
Two Positive Regions	1 or 2 positive regions on PET	Both regions negative on PET	NA	NA
One Positive Region; One Negative Region	PET is correct on positive region	Primary analysis: PET is negative on the positive region Secondary analysis: PET is negative on both regions only	Primary analysis: NA Secondary analysis: PET is negative on histopathology positive region and PET is positive on histopathology negative region	NA
Two Negative Regions	NA	NA	PET-positive on one or two regions	PET is negative on both regions

Source: BED-PSMA-301 Clinical Study Report (p.45)
Abbreviations: NA, not applicable; PET, positron emission tomography

An important secondary endpoint was patient-level VDR for distant metastases compared to a composite reference standard consisting of histopathology from surgery or biopsy of the metastatic site or confirmatory imaging obtained within 60 days after flotufolastat F 18 injection (originally to be performed within 45 days but time extended due to the COVID-19 pandemic). Patient-level VDR was initially planned to be the primary endpoint by the Applicant, but this was discussed in a meeting between the FDA and the Applicant on 7/19/2019 and it was agreed that this would be a secondary endpoint. A verified M1 metastasis required identification of a PET positive lesion in 1) a lymph node (or nodes) outside the pelvis, 2) soft

tissue/parenchyma, or 3) bones, that was confirmed as prostate cancer by histopathology or confirmatory imaging. Confirmatory imaging was reviewed by three central readers who were provided with a brief clinical summary and the flotufolastat F 18 PET imaging with annotations from the three independent reviewers, and who reached consensus for overall review assessment. Confirmatory imaging consisting of CT or MRI was considered positive for a visceral tumoral lesion if the lesion was ≥10 mm in longest dimension in the axial plane or if the reader was confident that the lesion represented a malignancy even if the size criterion was not met. Lymph nodes were considered positive on CT or MRI if they were ≥15 mm in short axis, ≥10 mm and <15 mm in the short axis but with secondary features such as a spherical rather than an ovoid shape, loss of a fatty hilum, contrast enhancement, and/or restricted diffusion (for MRI), or <10 mm if the reviewer was confident that it was positive for malignancy due to size increase and/or secondary features. Confirmatory imaging consisting of ultrasound was considered positive if the lesion had features such as a solid component, vascularity, low-resistance flow consistent with tumor vasculature, or growth in size. Confirmatory imaging consisting of ^{18}F-NaF PET bone imaging was interpreted based on SNMMI Practice Guidelines for Sodium ^{18}F-Fluoride PET/CT Bone Scans 1.0 while confirmatory imaging consisting of ^{18}F-fluciclovine PET was considered positive if lesions were less than 1 cm in diameter and had focal uptake greater than blood pool or were larger and had an uptake equal to or greater than bone marrow.

Statistical Analysis Plan

A statistical analysis plan was finalized and approved prior to study database lock. Definitions of populations used for analysis of data in this trial include:

- All Enrolled Patients = all patients who signed consent
- Full Analysis Set (FAS) = all patients who were scheduled to receive the flotufolastat F 18 injection having met inclusion/exclusion criteria
- Full Safety Population (FSP) = all patients who received the flotufolastat F 18 injection
- Efficacy Analysis Population (EAP) = all patients who received the flotufolastat F 18 injection with PET imaging, followed by RP and PLND
- Extended Efficacy Population (EEP) = all patients who received the flotufolastat F 18 injection with PET imaging; included M0 and M1 patients regardless of whether RP and PLND was performed; used for M1 efficacy and Kappa statistics
- Per Protocol Population for N1 (PPN) = all patients in the EAP with histopathology from surgery that allowed standard of truth (SoT) determination, without major protocol deviations that would influence the evaluation of the histopathology or PET scan
- Per Protocol Population for Extra-Pelvic Metastasis (PPM) = all patients in the EEP with no major protocol deviations, with either M0 disease or M1 disease confirmed by histopathology or confirmatory imaging of at least one lesion

The EAP was used for primary endpoint analysis, while the PPN was used for supportive analysis. The predefined sensitivity and sensitivity goals were 22.5% and 82.5%, respectively,

against which the lower bound of the 95% CI was compared. The study was considered successful if the sensitivity and specificity goals were met by at least the same two of three independent readers.

No formal interim analysis was performed.

Planned subgroup analyses (not involving formal hypothesis testing) were performed based on prostate cancer risk category, PSA value (most recent), race, and age groups.

Protocol Amendments

The initial BED-PSMA-301 protocol was dated 9/25/2019. No patients were enrolled under this original version of the protocol. There were two global amendments and two region-specific (Germany) amendments during the trial.

Amendment 1, Protocol v.2.0 dated 1/7/2020 clarified that baseline conventional imaging was required if not done in the 60 days prior to screening, clarified that assessment of endpoints and objectives was based on central BIE, clarified that the dose of flotufolastat F 18 could be 8 mCi +/- 20%, added an exploratory objective to "evaluate the number of PET-positive pelvic LNs by central BIE as compared to the number of pathologic positive LNs (by local histopathology analysis) in each region" with parallel endpoint evaluating the average number of PET positive pelvic LNs and average number of pathologic positive LNs in each region, added an interim look at the percent of pathologic N1 (pN1) and pathologic N0 (pN0) patients after 150 patients were enrolled, removed candidacy for primary treatment with EBRT as an inclusion criterion, changed the sample size to 375 from 300 and number of evaluable patients to 300 from 231, changed the number of positive and negative cases to 75 positive/225 negative from 58 positive/173 negative for termination of enrollment, updated the analysis sets including change of Modified Intent to Treat Population to EAP, and clarified that flotufolastat F 18 would be considered effective in detecting N1 disease if the co-primary endpoints were met by the same two out of three readers.

Amendment 2, Protocol v.3.0 dated 7/1/2020 made modifications due to the COVID-19 pandemic to extend the screening period, allow for combining of study visits, extend the period for the follow-up safety visit, and extend the time for follow-up procedures and scheduled RP and PLND to be completed. This amendment also clarified that patients must be treatment naive, excluded patients who had a known hypersensitivity to the active substance or any of the excipients of flotufolastat F 18, specified that pre-sacral LNs must be placed in a separate packet from other surgical specimens if collected and labeled "pre-sacral," increased the number of central readers for the flotufolastat F 18 PET scans from two to three, changed the time for start of imaging after flotufolastat F 18 injection from 50 to 90 minutes to 50 to 70 minutes, clarified that baseline conventional imaging must be performed at least 24 hours prior to the flotufolastat F 18 PET scan, modified and combined the last exploratory objective and endpoint to state that the diagnostic performance of flotufolastat F 18 will be assessed in patients with pelvic LN metastatic deposits <10 mm and ≥10 mm, and stated that dropout patients who failed to complete all study procedures for reasons other than adverse reactions

attributed to flotufolastat F 18 would be replaced, with no more than 15% of patients enrolled being replaced.

There were two Germany-specific protocol amendments. Amendment 1, Protocol v.2DE dated 6/20/2020 added details on the replacement of dropout patients, and excluded patients who had a known hypersensitivity to the active substance or any of the excipients of flotufolastat F 18. The second amendment, Protocol v.3.1DE, removed the text stating that remote consent and pre-screening via telephone were allowed since this was not permitted in Germany.

The original Statistical Analysis Plan (SAP) was dated 7/7/2020. There were three amendments to the SAP during the trial.

Amendment 1, SAP v2.0 dated 8/19/2021 renamed the overall decision of the readers from "consensus" to "majority" read, added that categories with low counts may be collapsed during the analysis of subcategories, removed the secondary objective and endpoint regarding exploration of the diagnostic performance of flotufolastat F 18 in patients with pelvic LN metastatic deposits <5 mm and ≥5 mm and metastatic deposits <10 mm and ≥10 mm, and updated the first exploratory endpoint to use cluster binary data estimation of confidence intervals.

Amendment 2, SAP v.3.0 dated 10/1/2021 updated the time period for treatment-emergent adverse events (TEAEs) from on or before Visit 3 to on or before Day 4.

Amendment 3, SAP v.4.0 dated 1/2/2022 added the PPM analysis population and renamed the original Per Protocol Population to Per Protocol Population for N1 lesions (PPN) while adding additional analyses, and added location mapping.

Of note, there were significant changes made between the final protocol and the final SAP including:

- Creation of the EEP and PPM
- Removal of the secondary exploratory objective and endpoint to evaluate diagnostic performance of flotufolastat F 18 in patients with pelvic LN metastatic deposits <5 mm and ≥5 mm and metastatic deposits <10 mm and ≥10 mm

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant indicated that the study was conducted in accordance with GCP and with oversight from site IRBs/IECs.

Financial Disclosure

One investigator who was the PI for Site (b) (6) had disclosable financial interests . The potential for bias related to this interest was minimized by the Applicant's use of an independent contract research organization to generate blinded PET reads. This investigator's site enrolled (b) (6) patients out of the total of 356 in the trial.

Patient Disposition

A total of 356 patients were enrolled in BED-PSMA-301, all of whom received flotufolastat F 18. These 356 patients represent the FAS and FSP. A total of 353 of these patients had a flotufolastat F 18 PET scan that could be evaluated, and 301 patients underwent the planned RP and PLND (including the 3 patients with a flotufolastat F 18 PET scan that could not be evaluated). Twenty patients were discontinued from the study, so a total of 336 patients completed the study; 1 of the 20 patients who did not complete the study did undergo a RP and PLND with an evaluable PET and pathology and is therefore included in the Efficacy Analysis Population, but was discontinued before study completion because of an "other" reason. Of the 301 patients who underwent the planned RP and PLND, 3 were excluded from the EAP because of missing flotufolastat F 18 PET imaging for central evaluation, and 2 patients who underwent RP and PLND did not have histopathology data, so the EAP consisted of 296 patients. Therefore, of the 356 patients who received the study drug, 55 patients did not undergo RP and PLND, and ultimately 60 of these patients in total were excluded from the EAP. The reasons for exclusion of these 60 patients are detailed in the table below.

Table 21. Patients Who Received Flotufolastat F 18 but Were Excluded From EAP

Reason for Lack of RP/PLND	Number of Subjects	%
M1	28	46.67
Subject declined surgery	13	21.67
M0 - other treatment	9	15.00
RP/PLND but patient excluded from EPSP and EAP	3	5.00
Missing reason	3	5.00
Missing RP/PLND data	2	3.33
Subject withdrew from study early	1	1.67
RP delayed	1	1.67
Total	**60**	

Source: Data provided by Applicant in response to FDA Statistical Reviewer information request
Abbreviations: EAP, efficacy analysis population; EPSP, evaluable PET scan population; PLND, pelvic lymph node dissection; RP, radical prostatectomy

Of the 20 patients who were discontinued, 3 withdrew from the study by choice, 3 decided on other treatment options (not otherwise specified), 2 decided to have focal ablation instead of surgery, 1 decided to have EBRT and 1 decided to have SBRT, 2 declined a biopsy or any other imaging, 1 withdrew because of an AE, 1 was lost to follow-up, 1 was discontinued because of physician decision, 1 had RP delayed, 1 discontinued because of Applicant decision due to an outdated follow-up timeline, 1 declined for financial reasons, 1 declined surgery or biopsy due to the COVID-19 pandemic, and 1 discontinued for an "other" reason.

The number of patients in the various analysis populations of BED-PSMA-301 are shown in the table below.

Table 22. BED-PSMA-301 Analysis Populations

Population	Total n (%)
FAS (full analysis set)	356 (100)
FSP (full safety population)	356 (100)
EAP[1] (efficacy analysis population)	296 (83.1)
EEP (extended efficacy population)	352 (98.9)
PPN (per protocol population for N1)	276 (77.5)
PPM (per protocol population for extra-pelvic metastasis)	335 (94.1)

Source: BED-PSMA-301 Clinical Study Report, Table 11
[1] 298 patients underwent RP+PLND, but 2 did not have histopathology data so the EAP included 296 patients

Protocol Violations/Deviations

The Applicant reported 58 major protocol deviations among 50 (14%) patients in the FAS. The most frequent major protocol deviations were related to procedures/tests (imaging not within 60 +/- 10 minutes excluded from PPN/PPM analysis, biopsy or follow-up more than 60 days after flotufolastat F 18 injection excluded from PPN analysis, baseline imaging more than 60 days before screening excluded from PPM analysis, flotufolastat F 18 PET scan performed but not available at (b) (4) CRO excluded from EEP analysis) occurring in 20 patients (5.6%) or the informed consent (date missing, document missing, signature missing), occurring in 18 patients (5.1%) for whom no action for the deviation was taken. Other major protocol deviations included patients with M0 disease not getting RP or EBRT for treatment in eight patients who were excluded from the EAP analysis, administered dose of flotufolastat F 18 injection outside the accepted range in five patients who were excluded from the PPN/PPM analysis, inclusion criteria of having unfavorable intermediate-risk, high-risk, or very high-risk disease not being met in four patients who were excluded from the PPN/PPM analysis, missing a study visit due to COVID-19 by one patient for whom no action was taken, receiving another PET imaging agent within 24 hours prior to flotufolastat F 18 PET scan by one patient who was excluded from the EEP analysis, and not being treatment naive at study entry (receiving focal laser ablation of prostate) for one patient.

These deviations could potentially impact the study results, but were mitigated by appropriate exclusion of patients with certain deviations from specific analysis populations.

Table of Demographic Characteristics

The demographic features of the patients in the FAS (same as the FSP), EAP, and PPN are summarized in Table 23. The mean age for the FAS was 64.9 years old, and 64.5 years old for the EAP and the PPN. The majority of the patients were White, and the percentage of Black or Hispanic/Latino subjects was somewhat lower than the proportion in the United States population per the 2022 Census estimates (Black ~8% in the trial vs. 13.6% in the general population, Hispanic/Latino ~5% vs. 18.9% (QuickFacts, 2022)).

Table 23. Demographic Characteristics of FAS, EAP, and PPN of BED-PSMA-301

Demographic Characteristic	FAS (n=356) n (%)	EAP (n=296) n (%)	PPN (n=276) n (%)
Age			
Mean years (SD)	64.9 (6.98)	64.5 (6.91)	64.5 (6.88)
Median (years)	65.0	65.0	65.0
Min, max (years)	46, 83	46, 82	46, 82
Age group			
<65 years	163 (45.8)	143 (48.3)	133 (48.2)
≥65 years	193 (54.2)	153 (51.7)	143 (51.8)
<75 years	328 (92.1)	279 (94.3)	262 (94.9)
≥75 years	28 (7.9)	17 (5.7)	14 (5.1)
Race			
White	289 (81.2)	243 (82.1)	228 (82.6)
Black or African American	30 (8.4)	24 (8.1)	22 (8.0)
Other[1]	4 (1.1)	1 (0.3)	1 (0.4)
Not Reported	33 (9.3)	28 (9.5)	25 (9.1)
Ethnicity			
Hispanic or Latino	17 (4.8)	15 (5.1)	13 (4.7)
Not Hispanic or Latino	311 (87.4)	255 (86.1)	238 (86.2)
Not Reported	28 (7.9)	26 (8.8)	25 (9.1)
Country			
United States	238 (66.9)	188 (63.5)	171 (62.0)
Finland	18 (5.0)	17 (5.7)	17 (6.2)
Germany	86 (24.2)	79 (26.7)	76 (27.5)
Netherlands	14 (3.9)	12 (4.1)	12 (4.3)

Source: BED-PSMA-301 Clinical Study Report, Table 12 and FDA Clinical Reviewer (Country)
[1] Other includes Asian, Native Hawaiian or Other Pacific Islander, and Other
Abbreviations: FAS, full analysis set; EAP, efficacy analysis population; PPN, per protocol population for N1; SD, standard deviation

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

Other important baseline characteristics for patients in the FAS, EAP, and PPN are detailed in Table 24 below. The T-stage, Gleason Grade Grouping (GGG), and PSA are used to risk stratify PC patients into risk groups. High or very high-risk patients were those who had either T3 or T4 disease, GGG 4 or 5 cancer, a primary Gleason pattern 5, or a PSA >20. Unfavorable intermediate-risk patients included those with GGG 3 cancer, GGG 2 disease with ≥50% of biopsy cores positive for PC, or >1 intermediate risk factor (T2b, T2c, PSA 10-20). More than half of the patients in the FAS (53.3%) had a GGG of 4 or 5; the GGG was the factor most likely to stratify a patient into the high or very high-risk grouping. Only a small percentage of patients in the FAS (15.8%) had T3 or T4 disease, and only about 18.3% of the patients had a PSA >20 that would stratify them into the high or very high-risk grouping.

All but one patient had baseline conventional imaging. A total of 213 (59.8%) of the patients in the FAS had a CT scan, 152 (42.7%) had a MRI, and 274 (77.0%) had a bone scan. A total of 5.9% of the FAS patients had evidence of pelvic lymph node metastases at the time of enrollment, while 5.6% had evidence of distant metastatic disease at enrollment.

Table 24. Other Baseline Characteristics of the FAS, EAP, and PPN of BED-PSMA-301

Baseline Characteristic	Parameter	FAS (n=356) n (%)	EAP (n=296) n (%)	PPN (n=276) n (%)
PSA	0 to 0.5	0	0	0
	>0.5 to 1.0	0	0	0
	>1.0 to 2.0	2 (0.6)	1 (0.3)	1 (0.4)
	>2.0 to 5.0	62 (17.4)	56 (18.9)	53 (19.2)
	>5.0 to 10.0	134 (37.6)	112 (37.8)	105 (38.0)
	>10.0 to 20.0	93 (26.1)	83 (28.0)	78 (28.3)
	>20.0	65 (18.3)	44 (14.9)	39 (14.1)
TNM T-stage	T1	145 (40.7)	121 (40.9)	110 (39.9)
	T2	134 (37.6)	112 (37.8)	106 (38.4)
	T3	54 (15.2)	45 (15.2)	43 (15.6)
	T4	2 (0.6)	1 (0.3)	1 (0.4)
	Tx	9 (2.5)	8 (2.7)	7 (2.5)
	Missing	12 (3.4)	9 (3.0)	9 (3.3)
Gleason grade grouping (GGG)	1	6 (1.7)	5 (1.7)	2 (0.7)
	2	50 (14.0)	42 (14.2)	38 (13.8)
	3	110 (30.9)	91 (30.7)	84 (30.4)
	4	87 (24.4)	78 (26.4)	77 (27.9)
	5	103 (28.9)	80 (27.0)	75 (27.2)
Risk category	High or very high-risk[1]	211 (59.3)	174 (58.8)	167 (60.5)
	Unfavorable Intermediate risk[2]	145 (40.7)	122 (41.2)	109 (39.5)
Baseline imaging status	Patients with baseline imaging	355 (99.7)	295 (99.7)	275 (99.6)
	Positive for pelvic lymph nodes	21 (5.9)	12 (4.1)	11 (4.0)
	Positive for distant metastases	20 (5.6)	14 (4.7)	13 (4.7)

Source: BED-PSMA-301 Clinical Study Report, Table 13 and Demographic Data Tables 14.1.5.2.1/14.1.5.2.2/14.1.5.2.3 and FDA Clinical Reviewer (PSA >10.0 to 20.0, PSA >20.0)
[1] High or Very High-Risk defined as meeting any of the criteria: T3 or T4, GGG 4 or 5, Primary Gleason pattern 5, or PSA >20
[2] Unfavorable Intermediate-Risk defined as any GGG 3, GGG 2 with ≥50% of biopsy cores positive for prostate cancer, or having >1 intermediate risk factor (T2b; T2c; PSA 10-20)
Abbreviations: EAP, efficacy analysis population; FAS, full analysis set; PPN, per protocol population for N1; PSA, prostate-specific antigen; TNM, tumor, node, metastasis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Drug compliance was not an issue in this study because flotufolastat F 18 was administered under the direct supervision of study personnel at clinical sites, and each administration volume and total radioactivity injected was verified.

Radiographic contrast agents or other PET agents <24 hours prior to the flotufolastat F 18 PET scan were prohibited, and initiation of any targeted or systemic therapy was not to occur until after histopathology was obtained for SoT assessment. Concurrent or prior history of ADT (including surgical orchiectomy, LHRH agonist/antagonist, anti-androgen alone or in combination with LHRH agonist/antagonist) was also not permitted in the study. Published data show that ADT may affect PSMA expression and uptake of PSMA PET radiotracers (Vaz, et al., 2020) (Afshar-Oromieh, et al., 2018).

As detailed above in the Patient Disposition section, 60 (16.9%) patients from the FAS/FSP (all of whom received flotufolastat F 18 and had PET imaging) did not undergo RP and PLND or otherwise did not have histopathology or an evaluable flotufolastat F 18 PET scan and were excluded from the EAP that was used for primary endpoint analysis. Half of these patients excluded from the EAP had M1 disease (n=30, 50%) based on local read of flotufolastat F 18 PET imaging. Notably, RP and PLND are not standard of care for patients with M1 disease. Slightly more than half of the excluded patients had N1 disease (n=31, 51.7%) based on local read of flotufolastat F 18 PET imaging. Of note, according to the primary efficacy analysis of the EAP, between 23-37 patients (7.8%-12.5%), depending on the reader, out of the 296 patients in the EAP had N1 disease detected on the BIE read of flotufolastat F 18 PET imaging, indicating that significantly more of the excluded patients had N1 disease per flotufolastat F 18 PET imaging than those in the primary analysis. Potential bias causing measured drug performance to be worse than true performance could be introduced from excluding these patients, since a significant number of patients with N1 or M1 disease on flotufolastat F 18 PET imaging could have had true positive pelvic LNs as well.

Efficacy Results – Primary Endpoint

The primary endpoint results for patient-level sensitivity and specificity are presented in Table 25. All three readers exceeded the predefined specificity goal of 82.5%, but none met or exceeded the predefined sensitivity goal of 22.5%. Majority read results reported here and elsewhere throughout this review were calculated by using the flotufolastat F 18 PET interpretation shared by at least two of the three readers. A known diagnostic issue of PSMA agents is low sensitivity due to the histopathology SoT used in these trials that can identify micrometastatic disease that is below the spatial resolution of available imaging modalities. This is likely a significant contributor to the low observed sensitivity.

Table 25. Patient-Level Sensitivity/Specificity for Detection of Pelvic Lymph Node Metastasis Compared to Surgical Pathology (EAP)

Diagnostic Performance Measure	Reader 1 N=296	Reader 2 N=296	Reader 3 N=296	Majority Read N=296
TP	21 (7.1%)	19 (6.4%)	16 (5.4%)	17 (5.7%)
FP	16 (5.4%)	14 (4.7%)	7 (2.4%)	9 (3.0%)
TN	210 (70.9%)	212 (71.6%)	219 (74.0%)	217 (73.3%)
FN	49 (16.6%)	51 (17.2%)	54 (18.2%)	53 (17.9%)
Specificity (TN/[TN+FP]) (%)	210/226 (92.9%)	212/226 (93.8%)	219/226 (96.9%)	217/226 (96.0%)
95% CI	88.8, 95.9	89.8, 96.6	93.7, 98.7	92.6, 98.2
p-value (H0: Specificity ≤82.5%)	<0.001	<0.001	<0.001	<0.001
Sensitivity (TP/[TP+FN]) (%)	21/70 (30.0%)	19/70 (27.1%)	16/70 (22.9%)	17/70 (24.3%)
95% CI	19.6, 42.1	17.2, 39.1	13.7, 34.4	14.8, 36.0
p-value (H0: Sensitivity ≤22.5%)	0.090	0.213	0.518	0.405

Source: BED-PSMA-301 Clinical Study Report, Table 14
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; FP, false negative; FP, false positive; PET, positron emission tomography; TN, true negative; TP, true positive

For patients with different categorizations among the regions, the Applicant's primary analysis used the prioritization of FN > FP to derive patient-level results from region-level data, rather than FP > FN, which was used in a secondary analysis. The FDA Clinical review team believes

that a FP > FN prioritization is more clinically relevant, since a FP designation could result in a patient being denied potentially curative treatment, and should have been used in the primary analysis. However, in the secondary analysis where the FP > FN prioritization was used, the data were found to be identical to the primary analysis since all patients who were recategorized were not in the EAP analysis set, and therefore also not in the PPN analysis set.

The performance of flotufolastat F 18 is based on patients who underwent RP and PLND with an evaluable PET scan and histopathology results available from the surgery (the EAP). As mentioned in the Patient Disposition section, 60 patients who received flotufolastat F 18 and were imaged were excluded from the EAP, and therefore the sensitivity and specificity values in Table 25 above are not based on evaluation of an intent-to-image population of 356 patients. An exploratory tipping point analysis for sensitivity was therefore performed. See Section 8.3 for additional detail. Based on this analysis, a disease positive rate (i.e., PPV) of 20% would result in two of the three readers having sensitivity values exceeding the pre-specified statistical threshold for success of 22.5%. A total of 28 of the 60 patients (46.67%) were excluded from the EAP because of M1 disease found on the flotufolastat F 18 PET scan, since they were no longer considered candidates for RP and PLND based on standard of care. These patients therefore did not have SoT histopathology results. Based on the natural history of prostate cancer, in which disease spreads from the prostate gland to pelvic lymph nodes, then to distant metastatic sites, patients with distant metastatic disease would most likely also harbor prostate cancer in pelvic lymph nodes. In fact, 31 out of the 60 patients (51.67%) excluded from the EAP had N1 disease identified on the flotufolastat F 18 PET scan. Thus, it seems likely that a significant number of patients who were excluded from the EAP may have had metastasis to pelvic lymph nodes that would have been identified if those patients had undergone RP and PLND. In conclusion, a 20% PPV is considered realistic for the 60 patients excluded, suggesting sensitivity for detecting pelvic lymph node metastasis may have exceeded the success criterion if RP and PLND had been conducted in all patients who received flotufolastat F 18 and were imaged.

A secondary endpoint for this trial was determination of the PPV for pelvic lymph node metastasis as compared to surgical pathology. The PPV was greater than 56% for all three readers, with a PPV of 65.4% for the majority read, as shown in Table 26. It is important to note that the PPV for all readers was greater than the percentage of patients found to have pelvic lymph node metastases on histopathology (70/296=23.6%), which is comparable to the prevalence of pelvic lymph node metastases in the general population of prostate cancer patients with unfavorable intermediate risk to very high-risk prostate cancer based on the literature (~5% for unfavorable intermediate-risk, ~17-23% for high-risk, ~47% for very high risk, with an average for a mixed population of these three risk groups of approximately 24%) (Rud, et al., 2022) (Kuperus, J. M.; Tobert, C. M.; Semerjian, A. M.; Qi, J.; Lane, B. R.; Michigan Urological Surgery Improvement Collaborative, 2022) (Reichard, et al., 2021). Because the PPV is higher than prevalence, flotufolastat F 18 PET adds diagnostic value in the group of patients who have a positive PET scan.

Table 26. Patient-Level PPV for Pelvic Lymph Node Metastasis Compared to Surgical Pathology

Diagnostic Performance Measure	Reader 1	Reader 2	Reader 3	Majority Read
	EAP			
	N=296	N=296	N=296	N=296
Number of patients with PET-positive finding in PLNs	37	33	23	26
TP	21 (56.8%)	19 (57.6%)	16 (69.6%)	17 (65.4%)
FP	16 (43.2%)	14 (42.4%)	7 (30.4%)	9 (34.6%)
PPV [95% CI]	21/37 (56.8%) [39.5, 72.9]	19/33 (57.6%) [39.2, 74.5]	16/23 (69.6%) [47.1, 86.8]	17/26 (65.4%) [44.3, 82.8]

Source: BED-PSMA-301 Clinical Study Report, modified Table 18
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PLN, pelvic lymph node; PPV, positive predictive value; TP, true positive

Demographic subgroup analyses based on age and race were performed. Analysis of the data based on sex could not be performed because only male patients were enrolled in this prostate cancer trial. No conclusions could be made regarding trends in sensitivity or specificity when the data were analyzed by race due to the small number of enrolled patients who were of races other than White. There were no discernable differences in sensitivity and specificity when the data were stratified by age groups <65 or ≥65, and <75 or ≥75, though the number in the ≥75 group was small (n=17).

Subgroup analyses of the co-primary endpoints were also performed to investigate the impact of risk factors on primary efficacy results. Patients enrolled in this trial included unfavorable intermediate-risk, as well as high and very high-risk prostate cancer patients. Data were stratified based on baseline PSA, NCCN risk group, and Gleason score.

Primary efficacy data were analyzed by baseline PSA, grouped in several ways. There was no clear trend in sensitivity or specificity for patients with PSA <10, PSA ≥10 or ≤20, or PSA >20, likely due to the fact that most patients had PSA <10 (56.4%) and a much smaller percentage had a PSA >20 (14.9%). However, when the co-primary endpoints were analyzed by the median PSA value (8.445), point estimates of sensitivity were higher for patients with PSA ≥8.445 than for patients with PSA <8.445, though the 95% CIs overlapped (Table 27 and Table 28). This likely reflects a trend for better performance with higher PSA values.

Table 27. Subgroup Analysis for Patients in EAP With PSA <8.445

Diagnostic Performance Measure	Reader 1 (N=148)	Reader 2 (N=148)	Reader 3 (N=148)
True positive	2 (1.4%)	3 (2.0%)	3 (2.0%)
False positive	8 (5.4%)	10 (6.8%)	3 (2.0%)
False negative	17 (11.5%)	16 (10.8%)	16 (10.8%)
True negative	121 (81.8%)	119 (80.4%)	126 (85.1%)
Sensitivity (%)	2/19 (10.5%)	3/19 (15.8%)	3/19 (15.8%)
(95% CI)	1.3% - 33.1%	3.4% - 39.6%	3.4% - 39.6%
Specificity (%)	121/129 (93.8%)	119/129 (92.2%)	126/129 (97.7%)
(95% CI)	88.1% - 97.3%	86.2% - 96.2%	93.4% - 99.5%
PPV	2/10 (20.0%)	3/13 (23.1%)	3/6 (50.0%)
(95% CI)	2.5% - 55.6%	5.0% - 53.8%	11.8% - 88.2%
NPV	121/138 (87.7%)	119/135 (88.1%)	126/142 (88.7%)
(95% CI)	81.0% - 92.7%	81.5% - 93.1%	82.3% - 93.4%

Diagnostic Performance Measure	Reader 1 (N=148)	Reader 2 (N=148)	Reader 3 (N=148)
Histopathology positive	19/148 (12.8%)	19/148 (12.8%)	19/148 (12.8%)
(95% CI)	7.9% - 19.3%	7.9% - 19.3%	7.9% - 19.3%

Source: Applicant analysis provided upon FDA Clinical Reviewer request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen

Table 28. Subgroup Analysis for Patients in EAP With PSA ≥8.445

Diagnostic Performance Measure	Reader 1 (N=148)	Reader 2 (N=148)	Reader 3 (N=148)
True positive	19 (12.8%)	16 (10.8%)	13 (8.8%)
False positive	8 (5.4%)	4 (2.7%)	4 (2.7%)
False negative	32 (21.6%)	35 (23.6%)	38 (25.7%)
True negative	89 (60.1%)	93 (62.8%)	93 (62.8%)
Sensitivity (%)	19/51 (37.3%)	16/51 (31.4%)	13/51 (25.5%)
(95% CI)	24.1% - 51.9%	19.1% - 45.9%	14.3% - 39.6%
Specificity (%)	89/97 (91.8%)	93/97 (95.9%)	93/97 (95.9%)
(95% CI)	84.4% - 96.4%	89.8% - 98.9%	89.8% - 98.9%
PPV	19/27 (70.4%)	16/20 (80.0%)	13/17 (76.5%)
(95% CI)	49.8% - 86.2%	56.3% - 94.3%	50.1% - 93.2%
NPV	89/121 (73.6%)	93/128 (72.7%)	93/131 (71.0%)
(95% CI)	64.8% - 81.2%	64.1% - 80.2%	62.4% - 78.6%
Histopathology positive	51/148 (34.5%)	51/148 (34.5%)	51/148 (34.5%)
(95% CI)	26.8% - 42.7%	26.8% - 42.7%	26.8% - 42.7%

Source: Applicant analysis provided upon FDA Clinical Reviewer request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PSA, prostate-specific antigen

There was also a difference noted in sensitivity when analyzing the data by NCCN risk groups, with a trend towards higher sensitivity in the high or very high-risk group when compared to the unfavorable intermediate risk group, particularly in two of the three readers (Table 29).

Table 29. Subgroup Analysis by NCCN Risk Group

NCCN Risk Group	Reader 1	Reader 2	Reader 3	Majority Read
High-risk or very high-risk				
Specificity (TN/[TN+FP]) (%)	135/146 (92.5)	136/146 (93.2)	140/146 (95.9)	139/146 (95.2)
95% CI	86.9%, 96.2%	87.8%, 96.7%	91.3%, 98.5%	90.4%, 98.1%
Sensitivity (TP/[TP+FN]) (%)	17/51 (33.3)	16/51 (31.4)	12/51 (23.5)	14/51 (27.5)
95% CI	20.8%, 47.9%	19.1%, 45.9%	12.8%, 37.5%	15.9%, 41.7%
Unfavorable intermediate-risk				
Specificity (TN/[TN+FP]) (%)	75/80 (93.8)	76/80 (95.0)	79/80 (98.8)	78/80 (97.5)
95% CI	86.0%, 97.9%	87.7%, 98.6%	93.2%, 100.0%	91.3%, 99.7%
Sensitivity (TP/[TP+FN]) (%)	4/19 (21.1)	3/19 (15.8)	4/19 (21.1)	3/19 (15.8)
95% CI	6.1%, 45.6%	3.4%, 39.6%	6.1%, 45.6%	3.4%, 39.6%

Source: BED-PSMA-301 Clinical Study Report, modified Table 26
Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; TN, true negative; TP, true positive

No clear trends in sensitivity or specificity were seen among patients with a Gleason Score of ≤6, 7, 8, 9, or 10, likely due to significant variance of the size of each group. When the data were stratified by Gleason score ≤7 or >7, there appeared to be a small trend towards increased

sensitivity in the Gleason score >7 group in at least two of the three readers (Table 30 and Table 31).

Table 30. Subgroup Analysis for Gleason Score ≤7 (EAP)

Diagnostic Performance Measure	Reader 1 (N=138)	Reader 2 (N=138)	Reader 3 (N=138)
True positive	8 (5.8%)	7 (5.1%)	7 (5.1%)
False positive	7 (5.1%)	4 (2.9%)	3 (2.2%)
False negative	24 (17.4%)	25 (18.1%)	25 (18.1%)
True negative	99 (71.7%)	102 (73.9%)	103 (74.6%)
Sensitivity (%)	8/32 (25.0%)	7/32 (21.9%)	7/32 (21.9%)
(95% CI)	11.5% - 43.4%	9.3% - 40.0%	9.3% - 40.0%
Specificity (%)	99/106 (93.4%)	102/106 (96.2%)	103/106 (97.2%)
(95% CI)	86.9% - 97.3%	90.6% - 99.0%	92.0% - 99.4%
PPV	8/15 (53.3%)	7/11 (63.6%)	7/10 (70.0%)
(95% CI)	26.6% - 78.7%	30.8% - 89.1%	34.8% - 93.3%
NPV	99/123 (80.5%)	102/127 (80.3%)	103/128 (80.5%)
(95% CI)	72.4% - 87.1%	72.3% - 86.8%	72.5% - 86.9%
Histopathology positive	32/138 (23.2%)	32/138 (23.2%)	32/138 (23.2%)
(95% CI)	16.4% - 31.1%	16.4% - 31.1%	16.4% - 31.1%

Source: Applicant analysis provided upon FDA Clinical Reviewer request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Table 31. Subgroup Analysis for Gleason Score >7 (EAP)

Diagnostic Performance Measure	Reader 1 (N=158)	Reader 2 (N=158)	Reader 3 (N=158)
True positive	13 (8.2%)	12 (7.6%)	9 (5.7%)
False positive	9 (5.7%)	10 (6.3%)	4 (2.5%)
False negative	25 (15.8%)	26 (16.5%)	29 (18.4%)
True negative	111 (70.3%)	110 (69.6%)	116 (73.4%)
Sensitivity (%)	13/38 (34.2%)	12/38 (31.6%)	9/38 (23.7%)
(95% CI)	19.6% - 51.4%	17.5% - 48.7%	11.4% - 40.2%
Specificity (%)	111/120 (92.5%)	110/120 (91.7%)	116/120 (96.7%)
(95% CI)	86.2% - 96.5%	85.2% - 95.9%	91.7% - 99.1%
PPV	13/22 (59.1%)	12/22 (54.5%)	9/13 (69.2%)
(95% CI)	36.4% - 79.3%	32.2% - 75.6%	38.6% - 90.9%
NPV	111/136 (81.6%)	110/136 (80.9%)	116/145 (80.0%)
(95% CI)	74.1% - 87.7%	73.3% - 87.1%	72.6% - 86.2%
Histopathology Positive	38/158 (24.1%)	38/158 (24.1%)	38/158 (24.1%)
(95% CI)	17.6% - 31.5%	17.6% - 31.5%	17.6% - 31.5%

Source: Applicant analysis provided upon FDA Clinical Reviewer request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Data Quality and Integrity

The inspection and review of select clinical investigators, the contract research organization that centrally evaluated flotufolastat F 18 PET imaging results, and select clinical sites by the FDA OSI did not reveal any GCP deficiencies.

As noted previously, one investigator who was the PI for Site (b) (6) (b) (6) had disclosable financial interests. There were (b) (6) patients enrolled from Site

(b) (6) with (b) (6) included in the EAP and (b) (6) patients enrolled from Site (b) (6) with (b) (6) included in the EAP. As shown in Table 32 the estimates of sensitivity and specificity for the EAP did not significantly change when the (b) (6) patients enrolled at these sites were excluded from the analysis.

Table 32. Patient-Level Sensitivity/Specificity for Detection of Pelvic Lymph Node Metastasis Compared to Surgical Pathology (EAP) Excluding Sites (b) (6)

Diagnostic Performance Measure	Reader 1 N=217	Reader 2 N=217	Reader 3 N=217	Majority Read N=217
True positive	14 (6.5%)	12 (5.5%)	10 (4.6%)	11 (5.1%)
False positive	14 (6.5%)	14 (6.5%)	6 (2.8%)	8 (3.7%)
False negative	31 (14.3%)	33 (15.2%)	35 (16.1%)	34 (15.7%)
True negative	158 (72.8%)	158 (72.8%)	166 (76.5%)	164 (75.6%)
Sensitivity (%) (95% CI)	14/45 (31.1%) [18.2% - 46.6%]	12/45 (26.7%) [14.6% - 41.9%]	10/45 (22.2%) [11.2% - 37.1%]	11/45 (24.4%) [12.9% - 39.5%]
Specificity (%) (95% CI)	158/172 (91.9%) [86.7% - 95.5%]	158/172 (91.9%) [86.7% - 95.5%]	166/172 (96.5%) [92.6% - 98.7%]	164/172 (95.3%) [91.0% - 98.0%]
PPV (95% CI)	14/28 (50.0%) [30.6% - 69.4%]	12/26 (46.2%) [26.6% - 66.6%]	10/16 (62.5%) [35.4% - 84.8%]	11/19 (57.9%) [33.5% - 79.7%]
NPV (95% CI)	158/189 (83.6%) [77.5% - 88.6%]	158/191 (82.7%) [76.6% - 87.8%]	166/201 (82.6%) [76.6% - 87.6%]	164/198 (82.8%) [76.8% - 87.8%]
Histopathology (95% CI)	45/217 (20.7%) [15.5% - 26.7%]	45/217 (20.7%) [15.5% - 26.7%]	45/217 (20.7%) [15.5% - 26.7%]	45/217 (20.7%) [15.5% - 26.7%]

Source: Applicant analysis provided upon FDA Clinical Reviewer request
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value

Efficacy Results – Secondary and Other Relevant Endpoints

The secondary endpoint for this trial was patient-level VDR for distant metastasis and the results are presented in Table 33. Data analysis was accomplished using the EEP, and no performance goal was set. The VDR ranged from 9.9% to 14.2% across the three readers. Unlike the analysis of sensitivity and specificity, this analysis included use of both histopathology and confirmatory imaging as SoT, though use of histopathology alone would have been ideal but not realistic. Only 3-5% of flotufolastat F 18 PET detected distant metastatic lesions had histopathology as SoT, and even with inclusion of both histopathology and imaging, approximately 40-58% (depending on the reader) of PET detected lesions did not have any SoT determination and were therefore classified as FP. The dependence on confirmatory imaging as SoT for a large number of lesions (36.9%-56.8% depending on the reader) could have resulted in a lower TP rate due to the fact that conventional imaging used for confirmation has less than optimal performance in detecting prostate cancer lesions; a lesion that was identified as positive on flotufolastat F 18 PET could have been labeled as FP incorrectly because the "SoT" was not accurate. This imputation of a large number of lesions as FP could have resulted in underestimation of the VDR for M1 disease.

Table 33. Detection Rate of M1 Disease Verified by Histopathology or Confirmatory Imaging in the EEP

Diagnostic Performance Measure	Reader 1 N=352	Reader 2 N=352	Reader 3 N=352	Majority Read N=352
TP	35 (9.9%)	50 (14.2%)	36 (10.2%)	34 (9.7%)
FP	21 (6.0%)	48 (13.6%)	27 (7.7%)	27 (7.7%)
Negative	296 (84.1%)	254 (72.2%)	289 (82.1%)	291 (82.7%)
VDR	35/352 (9.9%)	50/352 (14.2%)	36/352 (10.2%)	34/352 (9.7%)
[95% CI]	[7.0, 13.6]	[10.7, 18.3]	[7.3, 13.9]	[6.8, 13.2]

Source: BED-PSMA-301 Clinical Study Report, modified Table 16
Abbreviations: CI, confidence interval; EEP, extended efficacy population; FP, false positive; PET, positron emission tomography; TP, true positive; VDR, verified detection rate

When analyzed per region (lymph node(s) outside the pelvis, soft tissue/parenchyma, or bone), the VDR was highest in bone, ranging from 5.7% to 10.5% across the three readers.

Patient-level PPV for M1 lesions as determined by central BIE compared to SoT (histopathology or confirmatory imaging) was also assessed as a secondary endpoint (Table 34). The PPV ranged from 51.0% to 62.5% across the three readers.

Table 34. Patient-Level PPV for M1 Disease Compared to SoT in the EEP

Diagnostic Performance Measure	Reader 1 N=352	Reader 2 N=352	Reader 3 N=352	Majority Read N=352
Number of patients with PET-positive finding in extra-pelvic sites	56	98	63	61
TP	35 (62.5%)	50 (51.0%)	36 (57.1%)	34 (55.7%)
FP	21 (37.5%)	48 (49.0%)	27 (42.9%)	27 (44.3%)
PPV [95% CI]	35/56 (62.5%) [48.5, 75.1]	50/98 (51.0%) [40.7, 61.3]	36/63 (57.1%) [44.0, 69.5]	34/61 (55.7%) [42.4, 68.5]

Source: BED-PSMA-301 Clinical Study Report, modified Table 18
Abbreviations: CI, confidence interval; EEP, extended efficacy population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value; SoT, standard of truth; TP, true positive

An estimate of the prevalence of M1 disease in this trial population is difficult to make because the FN rate is unknown since metastatic lesions that were flotufolastat F 18 PET negative were not biopsied nor assessed with confirmatory imaging. Baseline conventional imaging may give a sense of the number of patients with metastatic disease at time of enrollment, though the performance of conventional imaging including CT, MRI, and bone scan is known to be sub-optimal. M1 disease was detected on baseline conventional imaging in 5.7% of the patients in the EEP, and can be used as a best-guess estimate of the prevalence of metastatic disease in this population. Since the PPV for all readers was considerably higher than the presumed prevalence of M1 disease in this trial, the test appears to have added diagnostic value in patients who tested positive.

Dose/Dose Response

A single dose of 8 mCi (296 MBq) +/- 20% of flotufolastat F 18 was administered to patients in this trial. The mean (+/- SD) total decay-corrected administered activity in the FAS/FSP was 8.3 +/- 0.62 mCi (306.9 +/- 22.98 MBq), with a range of 5.77 to 10.75 mCi (213.49 to 397.75 MBq). Two of the 356 patients (0.56%) in the FAS received a dose below the lower limit of 6.4 mCi; one received 6.03 mCi, while one received 5.77 mCi. Three patients (0.84%) received a dose

above the upper limit of 9.6 mCi; one received 9.8 mCi, one received 10.75 mCi, and one received 9.78 mCi.

See also Clinical Pharmacology Section 6.

Additional Analyses Conducted on the Individual Trial

The Applicant evaluated the percentage of patients upstaged to N1 or M1 disease. Upstaging to N1 disease was defined as the number of patients with no N1 disease on baseline conventional imaging who had at least one flotufolastat F 18 PET positive lesion confirmed by histopathology (TP) out of all patients with evaluable scans (EEP). Upstaging to M1 disease was defined as the number of patients with no M1 disease on baseline conventional imaging who had at least one flotufolastat F 18 PET positive lesion in an extra-pelvic site confirmed by histopathology or confirmatory imaging (TP) out of all patients with evaluable scans (EEP). Upstaging provides some evidence of the value of flotufolastat F 18 PET when compared to conventional imaging as it indicates PET detected TP lesions that conventional imaging missed. A total of 3.7%-5.1% of patients were upstaged to N1 disease, and 8.0%-12.2% of patients were upstaged to M1 disease depending on the reader.

Table 35. Percent of Patients Upstaged to N1 and M1 in the EEP

Change	Reader 1 (N=352)	Reader 2 (N=352)	Reader 3 (N=352)	Majority Read (N=352)
Upstaged to N1	18 (5.1%)	15 (4.3%)	13 (3.7%)	14 (4.0%)
Upstaged to M1	29 (8.2%)	43 (12.2%)	28 (8.0%)	27 (7.7%)

Source: BED-PSMA-301 14.2 Efficacy Data – Tables and Figures, Table 14.2.2.6
Abbreviations: EEP, extended efficacy population; PET, positron emission tomography

Inter-reader and intra-reader reproducibility were both examined for PET read results in the pelvic lymph nodes. Inter-reader reproducibility was assessed by using Fleiss' kappa statistic across the three readers, with the kappa value found to be 0.74 (95% CI 0.65-0.82), indicating substantial agreement among the readers. Intra-reader reproducibility was assessed through repeat reads on 70 randomly selected images by all three readers. Reader 2 and Reader 3 both had 95.7% agreement between the initial read and the second read for the pelvic lymph node region, while Reader 1 had a 94.3% agreement rate. Cohen's kappa was used to assess intra-reader agreement, and these ranged from 0.78-0.81, indicating at least substantial agreement between the initial and repeat reads.

8.1.3. BED-PSMA-302 (SPOTLIGHT)

Trial Design

BED-PSMA-302 (SPOTLIGHT) was a prospective, single-arm, open-label trial to assess the CDR and PPV of flotufolastat F 18 PET in detecting recurrent disease compared to a composite reference standard consisting of histopathology and imaging. The study was performed in the United States, Finland, and the Netherlands. Results from patients enrolled in Finland and the Netherlands should be applicable to the United States population.

This trial enrolled adult males who were suspected of having BCR of PC based on an elevated PSA following curative intent treatment per the AUA (PSA ≥0.2 ng/mL with a confirmatory value also ≥0.2 ng/mL after RP) or Phoenix criteria (nadir +2 ng/mL after EBRT, brachytherapy, of focal gland therapy, e.g., HIFU) and who were potentially eligible for salvage therapy. Patients with current ADT use or prior ADT within 16 weeks of screening were excluded. Patients were to have baseline conventional imaging consisting of planar and/or SPECT bone scan, CT or MRI of the abdomen/pelvis, CT of the chest, or PET with ^{18}F-sodium fluoride or ^{18}F-fluciclovine done within 90 days prior to enrollment (as part of standard of care) or between the screening visit up to 2 weeks after the day of administration of flotufolastat F 18, at least 24 hours apart from the flotufolastat F 18 PET scan. Historical conventional imaging, or imaging performed more than 90 days before enrollment but within the previous 24 months as part of the patient's management could be collected as well; historical imaging could be used with baseline imaging to establish SoT.

After enrollment, each patient was administered 8 mCi +/- 20% of flotufolastat F 18 intravenously. As discussed in Section 6 of this review, the dose was selected based on BED-PSMA-101 dosimetry data and research at the Technical University of Munich that identified the range of administered activity that would result in highest overall image quality. With the patient in a supine position with their arms above their heads (if feasible), PET/CT images of the skull base through mid-thigh were obtained 50-70 minutes after injection of flotufolastat F 18. The flotufolastat F 18 PET images were reviewed by one local reader at the study site who had been trained on the interpretation of flotufolastat F 18 images to determine if recurrent disease was present and to guide confirmation of PET-positive lesions with a biopsy or with imaging. Patients with recurrent disease as detected by the local read were to undergo further evaluation following an algorithm to confirm PET-positive findings. The preferred SoT was histopathology, and therefore Step 1 of the algorithm was to obtain an image-guided biopsy if safe and feasible for SoT determination. A biopsy was not required if a patient was planned to undergo surgical resection of any PET-positive lesions as part of standard of care. Biopsy or surgical resection of the PET-positive lesions was to occur within 60 days of the flotufolastat F 18 PET scan. If more than one site of recurrence was detected, then the most accessible and feasible lesion was to be biopsied in each region. Confirmation of at least one PET-positive lesion in each region was required. There were three regions defined in this study: 1) prostate/prostate bed, 2) pelvic lymph nodes (right and left external iliac, obturator, hypogastric [internal iliac], perirectal, and presacral lymph nodes), 3) other, to include bone, extra-pelvic lymph nodes, viscera, and other soft tissue. Soft tissue lesions were preferred over bone lesions, and lesion size was also considered when deciding on the feasibility of a biopsy since there could be high sampling error for small lesions.

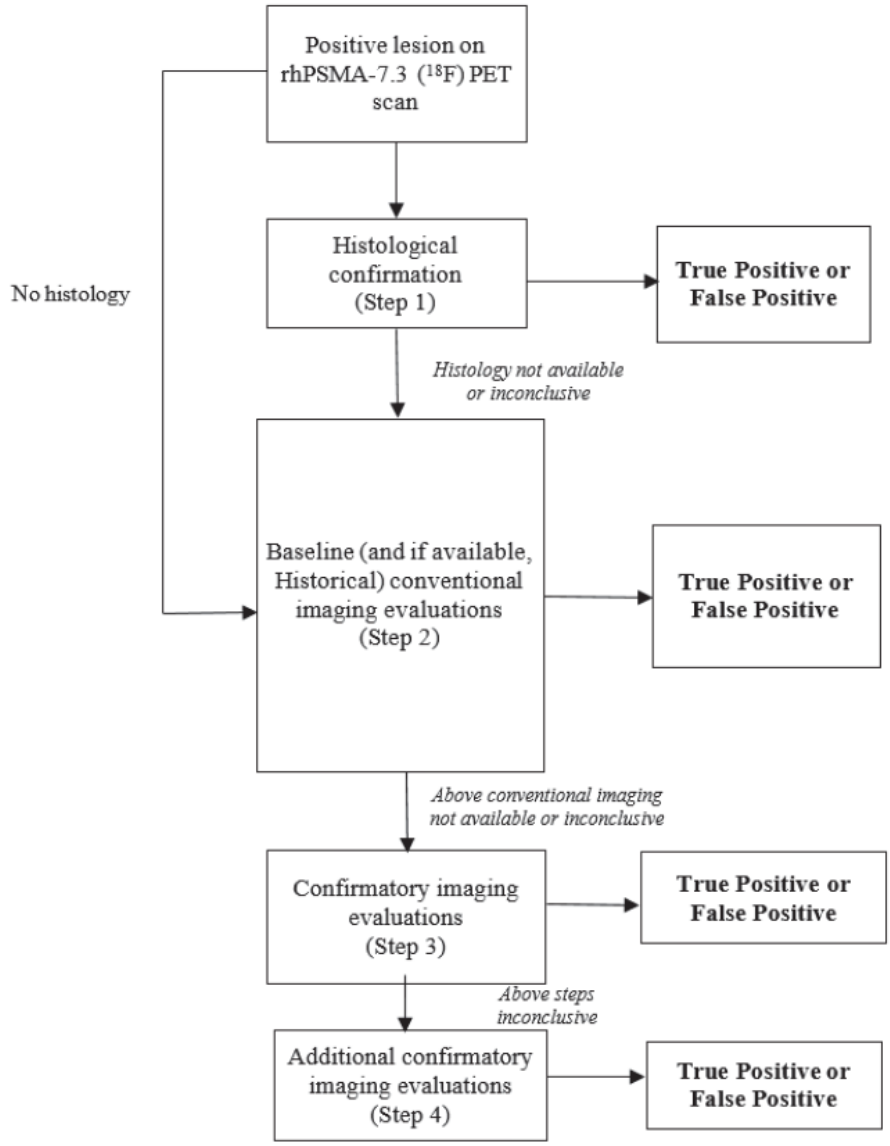
If it was not feasible to obtain histopathology or if the patient refused biopsy/surgery, then conventional imaging could be used for SoT determination to confirm positivity of the PET findings, following Steps 2-4 of the algorithm. Serial imaging over at least two timepoints, termed longitudinal imaging, was required for SoT imaging assessment to allow for use of change in lesion characteristics to determine presence of disease. Baseline imaging was required at time of enrollment or was obtained shortly after as per above. If historical imaging, defined as imaging obtained more than 90 days before enrollment within the past 24 months,

was available, then these images were used with baseline imaging for SoT determination as Step 2 in the algorithm. If historical imaging was not available, or review of historical imaging with baseline imaging was not sufficient to make a SoT determination, then confirmatory imaging, such as CT, MRI, ^{18}F-sodium fluoride or ^{18}F-fluciclovine PET, or bone scan was obtained (Step 3). These images were to be obtained within 60 days of the flotufolastat F 18 PET scan. If SoT determination could not be made with the confirmatory imaging, then additional confirmatory imaging to be performed up to 90 days after the flotufolastat F 18 PET scan could be acquired (Step 4).

All flotufolastat F 18 PET imaging and conventional imaging were submitted to the contract research organization, (b) (4) The PET images were presented to the readers in a randomized manner and were reviewed by three independent central readers who were blinded to all conventional imaging and clinical data. Three different central readers, named the SoT consensus panel, reviewed conventional imaging and were provided with a brief summary of clinical information and the flotufolastat F 18 PET images with annotations by the three independent PET readers for confirmation of lesion location only. These central reads of imaging were performed for assessment of the study endpoints. All central readers, like local readers, were trained in the interpretation of flotufolastat F 18 PET scans.

Vital signs were performed at screening and pre and post flotufolastat F 18 injection. AEs were recorded at every visit from the time of informed consent to the follow-up visit or until all confirmatory imaging visits were completed.

Figure 6. Guidance for the Standard of Truth Algorithm



Source: BED-PSMA-302 Clinical Study Report, Figure 2
Abbreviations: PET, positron emission tomography; rhPSMA-7.3, radiohybrid prostate-specific membrane antigen-7.3

Study Endpoints

The co-primary endpoints were patient-level CDR and region-level PPV of flotufolastat F 18 PET/CT for detection of recurrent PC compared to a composite reference standard consisting of histopathology and imaging. Patient-level CDR was defined as the percentage of all patients in the Efficacy Analysis Population (EAP), as defined further below, with at least one TP lesion regardless of any FP findings. The region-level PPV was defined as the number of TP regions out of all PET-positive regions in all imaged patients, which could include up to three regions per patient. The Applicant had originally proposed use of the patient-level PPV as a co-primary endpoint, but was recommended to use region-level PPV instead, since CDR and patient-level

PPV are more redundant. The region-level PPV endpoint was finally agreed upon in an Efficacy Information Amendment submitted by the Applicant on 1/13/2020.

Unlike in the setting of newly diagnosed prostate cancer, specificity is not a practical endpoint for trials involving patients with BCR because it is difficult to ascertain TN regions in this population without a long follow-up period and additional uncertainties. However, a PPV can impart some information related to the FP rate and is more practical to estimate. The CDR can complement the PPV value and is less reader dependent.

A co-localization approach was used to translate lesion-level findings to region-level findings. Three regions were defined in this study: 1) prostate/prostate bed, 2) pelvic lymph nodes, 3) other (including bone, extra-pelvic lymph nodes, viscera, and other soft tissue). During central PET reads, a systemic review of the PET images was performed starting in the prostate or prostatic bed, and positive lesions defined as those with "uptake greater than background and being consistent with prostate cancer" were identified. True positivity or true negativity was first determined at the lesion-level using histopathology or conventional imaging if histopathology was not available as SoT. Conventional imaging was reviewed by three central readers who were provided with a brief clinical summary and the flotufolastat F 18 PET imaging with annotations from the three independent PET reviewers, and who reached consensus for overall review assessment. Conventional imaging consisting of CT or MRI was considered positive for a visceral tumoral lesion if the lesion was ≥10 mm in longest dimension in the axial plane or if the reader was confident that the lesion represented a malignancy even if size criteria was not met. Lymph nodes were considered positive on CT or MRI if they were ≥15 mm in short axis, ≥10 mm and <15 mm in the short axis but with secondary features such as spherical rather than ovoid shape, loss of a fatty hilum, contrast enhancement, and/or restricted diffusion (for MRI), or <10 mm if the reviewer was confident of malignancy due to size increase and/or secondary features. Conventional imaging consisting of ^{18}F-NaF PET bone imaging was interpreted based on SNMMI Practice Guidelines for Sodium ^{18}F-Fluoride PET/CT Bone Scans 1.0, while conventional imaging findings on ^{18}F-fluciclovine PET were considered positive if they were less than 1 cm in diameter and had focal uptake greater than blood pool or were larger and had an uptake equal to or greater than bone marrow. Flotufolastat F 18 PET-positive regions without any corresponding SoT-positive lesions were considered FP regions. A flotufolastat F 18 PET-positive region with at least one corresponding SoT-positive lesion was considered a TP. Flotufolastat F 18 PET PET-negative regions with at least one SoT-positive lesions were considered FN regions. If a region had FN and FP lesions, it would be considered a FP region.

An important exploratory endpoint assessed in BED-PSMA-302 was the overall detection rate on a patient-level, which was defined as the proportion of flotufolastat F 18 PET PET-positive scans without regard to SoT confirmation over the total number of patients scanned. The detection rate is often reported for imaging modalities used for PC in the literature and is often presented as a function of PSA level; the detection rate typically increases with increasing PSA levels, and correlates with burden of disease. The detection rate is also sometimes considered as a rough estimate of test potential when truth standards are lacking in patients with suspected recurrence of PC.

Statistical Analysis Plan

A statistical analysis plan was finalized and approved prior to study database lock. Definitions of populations used for analysis of data in this trial include:

- All Enrolled Patients = all patients who signed consent
- Full Analysis Set (FAS) = all patients who were scheduled to receive the flotufolastat F 18 injection having met inclusion/exclusion criteria or who received the flotufolastat F 18 injection
- Full Safety Population (FSP) = all patients who received the flotufolastat F 18 injection
- Evaluable PET Scan Population (EPSP) = all patients who received the flotufolastat F 18 injection and a PET scan
- Efficacy Analysis Population (EAP) = all patients who received the flotufolastat F 18 injection followed by PET/CT scan for whom sufficient data is available to permit clear classification according to the SoT algorithm (included patients with no histopathology results and imaging from only one timepoint)
- Per Protocol Population (PP) = all patients in the EAP without major protocol deviations that could have affected the primary endpoint (excluded patients without histopathology or serial conventional imaging)

The EAP was used for primary endpoint analysis, and safety analysis was based on the FSP. The predefined patient-level CDR and region-level PPV goals were 36.5% and 62.5% respectively, against which the lower bound of the 95% CI was compared. The study was considered successful if the patient-level CDR and region-level PPV goals were met by at least the same two of three independent readers.

No formal interim analysis was performed.

Planned subgroup analyses were performed to determine the patient-level CDR and region-level PPV in patients with negative baseline conventional imaging and also in patients with and without SoT histopathology; data were also stratified based on PSA level. Subgroup analyses based on age and race were performed upon FDA Clinical Reviewer request.

Protocol Amendments

The initial BED-PSMA-302 protocol was dated 10/31/2019. No patients were enrolled under this original version of the protocol. There were three global amendments during the trial.

Amendment 1, Protocol v.2.0 dated 1/7/2020, clarified the definition of the co-primary endpoint of CDR, updated the co-primary endpoint of PPV to region-level analysis rather than patient-level analysis, added text to indicate that overall PPV will likely be decreased by patients with multiple PSMA PET positive regions, clarified secondary and exploratory endpoints, added details to stop enrollment of patients with PSA <1 ng/mL if the proportion exceeded 60% at planned interim analysis (later removed), added an Optional Visit 2a, clarified dose as 8 mCi +/- 20%, clarified key assumptions, edited inclusion criteria pertaining to an

elevated PSA to include nadir +2 ng/mL after focal therapy, updated diluted volumes of the investigational medicinal product (IMP) that can be used and the shelf life of the IMP, clarified wording regarding baseline and historical conventional imaging, added text for confirmatory imaging, edited the process for biopsy/surgery, edited the SoT algorithm, edited the central reading plan, clarified that the assessment of the impact on clinical management depended on the clinical utility questionnaire, clarified the timepoint for conventional imaging if historical imaging was done greater than 90 days before Visit 1, updated the sample size and number of evaluable patients needed before enrollment was to be stopped, updated the analysis sets, and added a planned interim analysis.

Amendment 2, Protocol v.3.0 dated 7/1/2020, extended the screening period if required due to the COVID-19 pandemic, allowed the combination of Visit 1 and Visit 2 due to COVID-19, allowed conventional imaging performed at non-participating institutions to be accepted, clarified that at least one PET-positive lesion in each region must be confirmed by histopathology or imaging in patients with multiple PET positive regions, added ability to delay biopsy or confirmatory imaging up to Day 60 due to the COVID-19, clarified the inclusion criteria regarding elevated PSA, added exclusion of patients with known hypersensitivity to active substance or excipient of the IMP, clarified that baseline conventional imaging was to be performed at least 24 hours apart from the investigational flotufolastat F 18 PET/CT, added definition of regions, clarified that the presence of one TP lesion in a region determines truth for the region regardless of any other FP lesions, increased the number of independent central PET readers from two to three, clarified that Visit 3 could be performed by any appropriately licensed and credentialed clinician and could be conducted by phone, clarified that serious adverse events (SAEs) should be reported immediately, detailed reasons why patient enrollment may be temporarily halted or stopped, added an option for remote study monitoring due to COVID-19, and clarified that Urgent Safety Measures may include amendments made due to the COVID-19 pandemic.

Amendment 3, Protocol v.4.0 dated 10/23/2020 removed the formal interim analysis, removed an exploratory objective and endpoint, and added BMI to demographic information obtained at screening.

The original Statistical Analysis Plan (SAP) was dated 7/7/2020. There were two amendments to the SAP during the trial.

Amendment 1, SAP v2.0 dated 7/22/2021 removed formal hypothesis testing at interim analysis, removed exploratory objective and endpoint #3, added BMI, clarified that the surgical Gleason score was preferred, clarified that the clinical TNM stage was preferred, added listings for SoT and summaries concerning SoT, added summaries of lesion size by reader, added listings for PET reads and SoT reads for readers who did not complete all reads, added that asymptotic normal was used for PPV CI and hypothesis testing, added logit transform using delta method for additional CI, added the EPSP analysis population, added Cohen's kappa at the region-level, changed analysis for AEs with missing grades such that any non-missing grade was considered worst, clarified the "other" region, added a shift table for heart rate, and added display of lesion size.

Amendment 2, SAP v3.0 dated 10/7/2021 extended the imputation rule for partial missing dates for time from initial diagnosis, updated the patient management plan section, clarified the plot of PSA against Study Days and regression calculation of PSAdt, clarified the rule for SoT determination, clarified that PET reader and location be included in all listings and tables, clarified that upstaging concerned patients with a negative scan at baseline, and updated time frame for TEAEs to on or before Day 7.

8.1.4. Study Results

Compliance With Good Clinical Practices

The Applicant indicated that the study was conducted in accordance with GCP and with oversight from site IRBs/IECs.

Financial Disclosure

The Applicant stated that no investigators had disclosable financial interests.

Patient Disposition

A total of 391 patients were enrolled in BED-PSMA-302 and received flotufolastat F 18. These 391 patients represent the FAS and FSP. 389 of these patients had an evaluable flotufolastat F 18 PET/CT scan and 369 completed SoT assessment, meaning that the SoT was assessed for all PET positive regions. Three patients were excluded from the primary analysis (two due to having ^{18}F-NaF PET scans performed on the same day as the flotufolastat F 18 PET/CT scan, and one because of missing imaging or histopathology for SoT determination), so a total of 366 patients were included in the EAP. Thirteen patients were discontinued, so a total of 378 patients completed the study. Of the 13 patients who discontinued, 2 were due to death, 1 was lost to follow-up, 1 was discontinued because of physician decision, 1 was discontinued due to protocol deviation, and 8 were discontinued due to "other" reasons.

Table 36. BED-PSMA-302 Analysis Populations

Population	Total n (%)
FAS (full analysis set)	391 (100)
FSP (full safety population)	391 (100)
EPSP (evaluable PET scan population)	389 (99.5)
EAP (efficacy analysis population)	366 (93.6)
PP (per protocol population)	288 (73.7)

Source: BED-PSMA-302 Clinical Study Report, Table 11
Abbreviations: PET, positron emission tomography

Protocol Violations/Deviations

The Applicant reported 300 protocol deviations in the FAS, 132 of which were minor deviations and 168 of which were considered major deviations. The 168 major protocol deviations were reported among 127 (32.5%) of the patients. The most frequent major protocol deviations involved procedures/tests (88 [22.5%]) and informed consent (40 [10.2%]). Eighty out of the 88

patients with a major protocol deviation that involved procedures/tests had conventional imaging at only one timepoint for SoT assessment, deviating from the protocol requirement of having longitudinal imaging, and were excluded from the PP. No action was taken for the patients who had deviations due to the informed consent. Other major protocol deviation that involved procedures/tests included imaging outside the 60 +/- 10 minute window and PET-positive lesions identified but not further investigated, all of whom were excluded from the PP. The other major protocol deviations included the recorded date of the biopsy being the date of report and not the actual procedure date in three patients for whom no action for the deviation was taken, follow-up biopsy performed more than 60 days after Visit 2 in two patients, baseline conventional imaging not performed 24 hours before Day 2 in two patients leading to exclusion from the EPSP, PSA value that did not meet inclusion criteria in five patients who were excluded from the PP, and flotufolastat F 18 dose below the lower limit of 6.4 mCi (6.22 mCi administered) in one patient who was excluded from the PP.

The large number of patients (80/391 [20.5%] of the FAS) who had conventional imaging from only a single timepoint to serve as SoT could potentially impact the study results. Given the unreliability of using one imaging timepoint as a SoT and the greater chance of not identifying a positive lesion when compared to longitudinal imaging over multiple timepoints, any PET-positive lesion that relied on conventional imaging at one timepoint for SoT may have been incorrectly labeled as a FP when in reality it should have been labeled as TP. This would negatively impact the patient-level CDR as well as the region-level PPV. This is further addressed in the Efficacy Results - Primary Endpoint section.

Table of Demographic Characteristics

The demographic features of the patients in the FAS (same as the FSP), EAP, and PP of the BED-PSMA-302 trial are summarized in Table 37. The mean age for the FAS was 68.3 years old, and 68.4 years old for the EAP and the PP. The patients enrolled in this trial were slightly older than those in the BED-PSMA-301 trial, which is expected since the BED-PSMA-302 trial enrolled patients in the recurrent setting versus at initial diagnosis in BED-PSMA-301. Most of the patients were White, and the percentage of Black subjects was comparable to the proportion in the United States population per 2022 Census estimates (Black ~15.6% in the trial vs. 13.6% in the general population (QuickFacts, 2022)). The percentage of Hispanic/Latino subjects was lower than the proportion in the United States population per 2022 Census estimates (Hispanic/Latino 4.6% vs. 18.9%). Overall, the demographics of both BED-PSMA-301 and BED-PSMA-302 are similar and comparable.

Table 37. Demographic Characteristics of Full Analysis Set, Efficacy Analysis Population, and Per Protocol Population of BED-PSMA-302

Demographic Characteristic	Full Analysis Set (n=391) n (%)	Efficacy Analysis Population (n=366) n (%)	Per Protocol Population (n=288) n (%)
Age			
Mean years (SD)	68.3 (7.92)	68.4 (7.86)	68.4 (7.88)
Median (years)	69.0	69.0	69.0
Min, max (years)	43, 86	43, 85	43, 85
Age group			
<65 years	121 (30.9)	112 (30.6)	91 (31.6)
≥65 years	270 (69.1)	254 (69.4)	197 (68.4)
≥75 years	90 (23.0)	86 (23.5)	66 (22.9)
Race			
White	295 (75.4)	276 (75.4)	214 (74.3)
Black or African American	61 (15.6)	61 (16.7)	49 (17.0)
Other[1]	14 (3.6)	11 (3.0)	11 (3.8)
Not Reported	21 (5.4)	18 (4.9)	14 (4.9)
Ethnicity			
Hispanic or Latino	18 (4.6)	17 (4.6)	11 (3.8)
Not Hispanic or Latino	342 (87.5)	320 (87.4)	252 (87.5)
Not Reported	31 (7.9)	29 (7.9)	25 (8.7)
Country			
United States	375 (95.9)	351 (95.9)	278 (96.5)
Finland	7 (1.8)	7 (1.9)	3 (1.1)
Netherlands	9 (2.3)	8 (2.2)	7 (2.4)

Source: BED-PSMA-302 Clinical Study Report, Table 12 and FDA Clinical Reviewer (Country)
[1] Other includes American Indian or Alaska Native, Asian, and Other
Abbreviations: SD, standard deviation

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

Other important baseline characteristics for patients in the FAS, EAP, and PP of the BED-PSMA-302 trial are detailed in Table 38 below. The median PSA value was 1.110 ng/mL in the FAS, 1.270 ng/mL in the EAP, and 1.600 ng/mL in the PP. Almost 80% of patients were treated with radical prostatectomy as definitive therapy for their initial PC diagnosis, while approximately 20% received radiation therapy as definitive treatment. Of note, approximately 40% of the patients had T3 disease at initial diagnosis, meaning more advanced disease with extracapsular extension or seminal vesicle involvement. This is expected since patients who present with more advanced disease have a greater chance of recurrence. About 27% of the population had a GGG of 4 or 5 at initial diagnosis, which would put them in at least the high-risk grouping.

Although baseline conventional imaging was to be obtained per protocol, only 96.7% of the FAS had such imaging. Local investigator interpretation of baseline conventional imaging identified recurrent disease in 21.2% of the FAS population at the time of enrollment.

Table 38. Other Baseline Characteristics of the Full Analysis Set, Efficacy Analysis Population, and Per Protocol Population of BED-PSMA-302 (SPOTLIGHT)

Baseline Characteristics Parameter	Full Analysis Set (n=391) n (%)	Efficacy Analysis Population (n=366) n (%)	Per Protocol Population (n=288) n (%)
PSA			
Mean (SD)	3.777 (9.5742)	3.954 (9.8494)	4.318 (10.0866)
Median	1.110	1.270	1.600
Range	0.03, 134.60	0.03, 134.60	0.10, 134.60
<0.5	121 (30.9)	105 (28.7)	69 (24.0)
≥0.5 to <1.0	67 (17.1)	63 (17.2)	48 (16.7)
≥1.0 to <2.0	45 (11.5)	43 (11.7)	36 (12.5)
≥2.0 to <5.0	90 (23.0)	88 (24.0)	76 (26.4)
≥5.0 to <10.0	36 (9.2)	36 (9.8)	30 (10.4)
≥10.0	32 (8.2)	31 (8.5)	29 (10.1)
TNM T-stage			
T1	58 (14.8)	57 (15.6)	47 (16.3)
T2	140 (35.8)	131 (35.8)	96 (33.3)
T3	160 (40.9)	146 (39.9)	121 (42.0)
T4	2 (0.5)	2 (0.5)	2 (0.7)
Tx	7 (1.8)	7 (1.9)	6 (2.1)
Missing	24 (6.1)	23 (6.3)	16 (5.6)
Gleason grade grouping (GGG)			
1	39 (10.0)	39 (10.7)	29 (10.1)
2	104 (26.6)	95 (26.0)	73 (25.3)
3	116 (29.7)	111 (30.3)	85 (29.5)
4	41 (10.5)	36 (9.8)	28 (9.7)
5	64 (16.4)	59 (16.1)	55 (19.1)
Missing	27 (6.9)	26 (7.1)	18 (6.3)
Prior therapy			
Radical prostatectomy	307 (78.5)	283 (77.3)	221 (76.7)
RP w/ radiation therapy	138 (35.3)	126 (34.4)	109 (37.8)
Radiation therapy alone	76 (19.4)	75 (20.5)	61 (21.2)
Other[1]	7 (1.8)	7 (1.9)	5 (1.7)
None	1 (0.3)	1 (0.3)	1 (0.3)
Baseline imaging status			
Patients with baseline imaging	378 (96.7)	355 (97.0)	280 (97.2)
Positive	83 (21.2)	80 (21.9)	71 (24.7)
Negative	270 (69.1)	250 (68.3)	189 (65.6)
Indeterminate	25 (6.4)	25 (6.8)	20 (6.9)

Source: Adapted from BED-PSMA-302 Clinical Study Report, Table 13, Table 14, Table 16 and Demographic Data Tables 14.1.5.2, FDA Clinical Reviewer

[1] Other includes cryotherapy, HIFU, prostate ablation, other

Abbreviations: PSA, prostate-specific antigen; RP, radical prostatectomy; SD, standard deviation; TNM, tumor, node, metastasis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Drug compliance was not an issue in this study because flotufolastat F 18 was administered under the direct supervision of study personnel at clinical sites.

Though the inclusion/exclusion criteria for BED-PSMA-302 stated that patients would be excluded if they were currently receiving ADT or if they had not been discontinued from ADT at least 16 weeks prior to screening, per the Applicant, three patients may have been on ADT at

the time the flotufolastat F 18 PET/CT was performed since a start date for ADT was captured but not a stop date. As previously discussed, ADT may affect the expression of PSMA and uptake of PSMA imaging agents.

As noted in the Protocol Violations/Deviations section, a significant number of patients (20.5%) did not have longitudinal imaging for SoT determination, and only had imaging from one timepoint for SoT determination. Of the 366 patients in the EAP population used for primary analysis of the co-primary endpoints, 73 patients had a SoT based on imaging from one timepoint only rather than determined by longitudinal conventional imaging or histopathology. The potential impact of these patients without histopathology or longitudinal conventional imaging were examined by exploratory analyses below. Also, see statistical issues in Section 8.3.

Efficacy Results – Primary Endpoint

The primary endpoint results for patient-level CDR and region-level PPV are presented in Table 39. The lower bound of the 95% CI for patient-level CDR exceeded the predefined threshold of 36.5% for all three readers, ranging from 46.1% to 48.4%. However, none of the lower bound of the 95% CIs met the predefined region-level PPV threshold of 62.5%, with the lower bound of these 95% CIs ranging from 42.0% to 55.1% across all three readers.

Table 39. Patient-Level CDR and Region-Level PPV (EAP)

Level/Region	Diagnostic Performance Measure	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366
Patient-level CDR	CDR	198/366 (54.1%)	188/366 (51.4%)	189/366 (51.6%)	208/366 (56.8%)
	95% CI	48.8, 59.3	46.1, 56.6	46.4, 56.9	51.6, 62.0
	p-value (H0: CDR ≤36.5%)	<0.0001	<0.0001	<0.0001	<0.0001
Region-level PPV					
All three regions (prostate/ prostate bed, pelvic lymph nodes, other [extra-pelvic] sites)	TP	247/535 (46.2%)	231/383 (60.3%)	226/430 (52.6%)	249/417 (59.7%)
	FP	288/535 (53.8%)	152/383 (39.7%)	204/430 (47.4%)	168/417 (40.3%)
	PPV	46.2%	60.3%	52.6%	59.7%
	95% CI	42.0, 50.3	55.1, 65.5	47.6, 57.5	54.7, 64.7
	p-value (H0: PPV ≤62.5%)	1.0000	0.7954	1.0000	0.8612

Source: BED-PSMA-302 Clinical Study Report, Table 17
Abbreviations: CDR, correct detection rate; CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value

During the review period, the clinical review team and the Applicant agreed that for calculation of patient-level CDR, the EPSP is more appropriate than the EAP as the denominator (i.e., 389 patients rather than 366). With the EPSP as the denominator, patient-level CDR is the percentage of patients with at least one TP lesion out of all patients who had an evaluable flotufolastat F 18 PET scan, regardless of positive or negative PET interpretation, availability of reference standard information, or FP results. By this preferred calculation, patient-level CDR

was 50.9% (95% CI: 45.8% to 56.0%) for reader 1, 48.3% (95% CI: 43.3% to 53.4%) for reader 2, and 48.6% (95% CI: 43.5% to 53.7%) for reader 3, and the majority read result was 48.6% (95% CI: 43.5% to 53.7%). The lower bound of the 95% CI for patient-level CDR using the preferred calculation still exceeded the predefined threshold of 36.5% for all three readers. (b) (4) (b) (4) However, for the remainder of Section 8.1.4 of this review, reported patient-level CDR analyses were performed using the originally pre-specified EAP population.

Since the primary region-level PPV endpoint combined all three regions together, an additional analysis to stratify the PPV by specific region in the EAP was performed to assess for variations between the regions. Sub-regions for the "other" region categorization were also evaluated. Using the point estimate, a relatively lower PPV for the "prostate/prostate bed" and "other: soft parenchyma" regions was seen.

Table 40. Region-Level PPV by Specific Region (EAP)

Region	Diagnostic Performance Measure	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366
Prostate/ Prostate bed	TP	61/255 (23.9%)	48/100 (48.0%)	50/147 (34.0%)	57/145 (39.3%)
	FP	194/255(76.1%)	52/100 (52.0%)	97/147 (66.0%)	88/145 (60.7%)
	PPV	23.9%	48.0%	34.0%	39.3%
	(95% CI)	(18.7, 29.2)	(38.2, 57.8)	(26.3, 41.7)	(31.3, 47.3)
Pelvic lymph nodes	TP	79/127 (62.2%)	71/111 (64.0%)	82/138 (59.4%)	80/117 (68.4%)
	FP	48/127 (37.8%)	40/111 (36.0%)	56/138 (40.6%)	37/117 (31.6%)
	PPV	62.2%	64.0%	59.4%	68.4%
	(95% CI)	(53.7, 70.7)	(55.0, 72.9)	(51.2, 67.6)	(59.9, 76.8)
Other (Extra-pelvic) sites[1]	TP	107/153 (69.9%)	112/172 (65.1%)	94/145 (64.8%)	112/155 (72.3%)
	FP	46/153 (30.1%)	60/172 (34.9%)	51/145 (35.2%)	43/155 (27.7%)
	PPV	69.9%	65.1%	64.8%	72.3%
	(95% CI)	(62.6, 77.2)	(58.0, 72.3)	(57.0, 72.6)	(65.2, 79.3)
Other: Lymph nodes outside of pelvis	TP	53/87 (60.9%)	47/74 (63.5%)	45/73 (61.6%)	50/75 (66.7%)
	FP	34/87 (39.1%)	27/74 (36.5%)	28/73 (38.4%)	25/75 (33.3%)
	PPV	60.9%	63.5%	61.6%	66.7%
	(95% CI)	(50.6, 71.2)	(52.5, 74.6)	(50.4, 72.9)	(55.9, 77.4)
Other: Soft tissue/ parenchyma	TP	5/19 (26.3%)	5/13 (38.5%)	4/11 (36.4%)	5/15 (33.3%)
	FP	14/19 (73.7%)	8/13 (61.5%)	7/11 (63.6%)	10/15 (66.7%)
	PPV	26.3%	38.5%	36.4%	33.3%
	(95% CI)	(6.0, 46.7)	(10.9, 66.0)	(6.5, 66.2)	(8.6, 58.0)
Other: Bones	TP	58/73 (79.5%)	74/125 (59.2%)	57/90 (63.3%)	67/95 (70.5%)
	FP	15/73 (20.5%)	51/125 (40.8%)	33/90 (36.7%)	28/95 (29.5%)
	PPV	79.5%	59.2%	63.3%	70.5%
	(95% CI)	(70.1, 88.8)	(50.5, 67.9)	(53.3, 73.3)	(61.3, 79.7)

Source: BED-PSMA-302 Clinical Study Report, Table 19

[1] Positive for any patient where one or more sub-region is positive. Thus, values are not a direct summation of the values for other: lymph nodes outside of pelvis, soft tissue/parenchyma, and bones.

Abbreviations: CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value; TP, true positive

Per the Applicant, the development of the statistical thresholds used an assumption that about 50% of the patients would have histopathology as the SoT in order to limit a reliance predominantly on conventional imaging for SoT determination. Conventional imaging is considered inferior to histopathology in determining "truth," especially conventional imaging at

one timepoint. Unfortunately, due to the COVID-19 pandemic during which the trial was conducted, the number of patients who were able to undergo biopsy or surgery for SoT determination was much less than anticipated. Overall, only 69 patients (18.9%) in the EAP had histopathology as the SoT, and 297 patients (81.1%) had imaging as the SoT. The ability to obtain longitudinal imaging for SoT determination was also likely affected, given the reluctance of patients to return to the clinic for confirmatory imaging as needed. As a result, 73 patients out of 366 patients (19.9%) with positive flotufolastat F 18 PET scans did not have histopathology or longitudinal imaging, and relied on conventional imaging from one timepoint for the SoT. Because of the low sensitivity of conventional imaging for detection of prostate cancer lesions, some flotufolastat F 18 PET-positive lesions may have been incorrectly classified as FP because they were not confirmed by conventional imaging. Thus, the measured performance of flotufolastat F 18 could have been affected with the calculated PPV being lower than reality. Imputation methods for these 73 patients without histopathology or longitudinal imaging were performed. Please see the Section 8.3 Statistical Issues for further details on these imputations and analyses.

To evaluate the possible impact of major protocol deviations on the efficacy results, including the 73 patients with no pathology or longitudinal conventional imaging for SoT determination, an analysis of region-level PPV in the PP was performed. While the region-level PPV ranged from 51.6%-64.9%, increased by approximately 4%-5% compared to analysis in the EAP, the region-level PPV still did not reach the predefined region-level PPV threshold of 62.5% for any of the three readers when considering the lower bound of the 95% CI.

Table 41. Region-Level PPV Excluding Patients with Major Protocol Deviations Such as Missing SoT Data (PP)

Level/Region	Diagnostic Performance Measure	Reader 1 N=288	Reader 2 N=288	Reader 3 N=288	Majority Read N=288
Region-level PPV					
All three regions (prostate/prostate bed, pelvic lymph nodes, other [extra-pelvic] sites)	TP	221/428 (51.6%)	211/325 (64.9%)	206/357 (57.7%)	224/349 (64.2%)
	FP	207/428 (48.4%)	114/325 (35.1%)	151/357 (42.3%)	125/349 (35.8%)
	PPV	51.6%	64.9%	57.7%	64.2%
	95% CI	47.1, 56.2	59.5, 70.4	52.4, 63.0	58.9, 69.5
	p-value (H0: PPV ≤62.5%)	1.0000	0.1912	0.9608	0.2664

Source: Modified from BED-PSMA-302 Clinical Study Report, Table 18
Abbreviations: CI, confidence interval; FP, false positive; PET, positron emission tomography; PP, per protocol; PPV, positive predictive value; SoT, standard of truth; TP, true positive

To further evaluate the effect of SoT on efficacy results, patient-level CDR and region-level PPV analysis was performed in patients with and without histopathology as SoT. For patients with histopathology, the patient-level CDR was 22%-25% higher than in the full EAP patient population, while patients without histopathology had a patient-level CDR that was 5%-6% lower than the full EAP. In terms of region-level PPV, the patients with histopathology had PPV point estimates between 60.9%-67.0% across the three readers, 7-15% higher than the full EAP

but still below the pre-specified threshold of 62.5% when considering the lower bound of the 95% CI; the patients without histopathology had PPVs 3%-4% lower than the full EAP. The readers are referred to Section 8.3 regarding the definition the Applicant used to report the majority read on region-level PPV in subjects with histopathology available as SoT.

Table 42. Analysis of Data by Availability of Histopathology as SoT (EAP)

		Histopathology Available as SoT				Histopathology Not Available as SoT			
Level/Region	Diagnostic Performance Measure	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366
Patient-level CDR	CDR	52/69 (75.4%)	53/69 (76.8%)	51/69 (73.9%)	56/69 (81.2%)	146/297 (49.2%)	135/297 (45.5%)	138/297 (46.5%)	152/297 (51.2%)
	95% CI	63.5, 84.9	65.1, 86.1	61.9, 83.7	69.9, 89.6	43.3, 55.0	39.7, 51.3	40.7, 52.3	45.3, 57.0
Region-level PPV									
All three regions (prostate/ prostate bed, pelvic lymph nodes, other)	TP	67/110 (60.9%)	69/103 (67.0%)	62/99 (62.6%)	73/102 (71.6%)	180/425 (42.4%)	162/280 (57.9%)	164/331 (49.5%)	176/315 (55.9%)
	FP	43/110 (39.1%)	34/103 (33.0%)	37/99 (37.4%)	29/102 (28.4%)	245/425 (57.6%)	118/280 (42.1%)	167/331 (50.5%)	139/315 (44.1%)
	PPV (95% CI)	60.9% (52.0, 69.8)	67.0% (57.6, 76.4)	62.6% (53.5, 71.8)	71.6% (62.5, 80.7)	42.4% (37.7, 47.0)	57.9% (51.7, 64.0)	49.5% (43.8, 55.3)	55.9% (50.0, 61.8)

Source: BED-PSMA-302 Clinical Study Report, Modified Table 21

Abbreviations: CDR, correct detection rate; CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value; SoT, standard of truth; TP, true positive

Because patients with N1 or M1 findings on baseline imaging were enrolled in this trial, an analysis of the co-primary endpoints was also performed in the subgroup of patients with negative conventional baseline imaging. In total, 250 patients in the EAP had negative conventional imaging and the patient-level CDR was approximately 6-8% lower for these patients with negative conventional imaging than for the full EAP population; the region-level PPV was approximately 4-6% lower than that for the full EAP population. The lower endpoint results in this analysis are likely driven by the removal of patients with more readily detected disease since they had N1 or M1 findings that could be seen on conventional imaging.

Table 43. Analysis of Data in Patients with Negative Baseline Conventional Imaging (EAP)

Level/Region	Diagnostic Performance Measure	Reader 1 N=250	Reader 2 N=250	Reader 3 N=250	Majority Read N=250
Patient-level CDR	CDR	117/250 (46.8%)	113/250 (45.2%)	114/250 (45.6%)	126/250 (50.4%)
	95% CI	40.5, 53.2	38.9, 51.6	39.3, 52.0	44.0, 56.8
Region-level PPV: all three regions (prostate/ prostate bed, pelvic lymph nodes, other [extra-pelvic] sites)	TP	141/355 (39.7%)	132/235 (56.2%)	130/278 (46.8%)	146/266 (54.9%)
	FP	214/355 (60.3%)	103/235 (43.8%)	148/278 (53.2%)	120/266 (45.1%)
	PPV	39.7%	56.2%	46.8%	54.9%
	(95% CI)	(34.6, 44.9)	(49.6, 62.7)	(40.7, 52.9)	(48.4, 61.3)

Source: BED-PSMA-302 Clinical Study Report, Table 20
Abbreviations: CDR, correct detection rate; CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value; TP, true positive

Patient-level CDR and region-level PPV data were also stratified by PSA, since detection rates vary depending on PSA levels with PSMA PET agents, particularly in the recurrent setting (Fendler, et al., 2019) (Perera, et al., 2020). There appears to be a general trend towards increasing patient-level CDR with increasing PSA, except in the PSA ≥5.0 to <10 group. There is also a trend towards increasing region-level PPV with increasing PSA, except in the PSA ≥10.0 group.

Table 44. Efficacy by PSA (EAP)

Level/Region	Diagnostic Performance Measure	Reader	PSA <0.5	0.5≤PSA <1.0	1.0≤PSA <2.0	2.0≤PSA <5.0	5.0≤PSA <10.0	PSA ≥10.0
Patient-level CDR	CDR (95% CI)	Reader 1 (N=366)	31/105 (29.5%) (21.0, 39.2)	28/63 (44.4%) (31.9, 57.5)	28/43 (65.1%) (49.1, 79.0)	64/88 (72.7%) (62.2, 81.7)	22/36 (61.1%) (43.5, 76.9)	25/31 (80.7%) (62.5, 92.5)
		Reader 2 (N=366)	25/105 (23.8%) (16.0, 33.1)	26/63 (41.3%) (29.0, 54.4)	28/43 (65.1%) (49.1, 79.0)	62/88 (70.5%) (59.8, 79.7)	21/36 (58.3%) (40.8, 74.5)	26/31 (83.9%) (66.3, 94.5)
		Reader 3 (N=366)	27/105 (25.7%) (17.7, 35.2)	29/63 (46.0%) (33.4, 59.1)	27/43 (62.8%) (46.7, 77.0)	61/88 (69.3%) (58.6, 78.7)	21/36 (58.3%) (40.8, 74.5)	24/31 (77.4%) (58.9, 90.4)
		Majority (N=366)	33/105 (31.4%) (22.7, 41.2)	31/63 (49.2%) (36.4, 62.1)	28/43 (65.1%) (49.1, 79.0)	68/88 (77.3%) (67.1, 85.5)	22/36 (61.1%) (43.5, 76.9)	26/31 (83.9%) (66.3, 94.5)
Region-level PPV								
All three regions (prostate/ prostate bed, pelvic lymph nodes, other)	PPV (95% CI)	Reader 1 (N=366)	29.1% (20.5, 37.7)	37.1% (27.6, 46.6)	45.6% (35.1, 56.1)	57.7% (50.1, 65.3)	57.9% (44.9, 70.9)	59.6% (47.6, 71.7)
		Reader 2 (N=366)	50.8% (36.9, 64.8)	51.8% (38.9, 64.6)	57.4% (43.7, 71.1)	65.0% (55.3, 74.6)	71.7% (56.8, 86.7)	62.7% (50.6, 74.9)
		Reader 3 (N=366)	34.5% (24.0, 45.0)	45.1% (33.5, 56.7)	52.5% (38.7, 66.2)	64.9% (55.9, 73.9)	58.7% (41.5, 75.9)	60.8% (47.3, 74.2)
		Majority (N=366)	45.9% (33.8, 58.1)	51.4% (39.1, 63.7)	55.2% (41.9, 68.5)	68.7% (59.7, 77.7)	71.4% (54.5, 88.4)	64.7% (52.2, 77.2)

Source: BED-PSMA-302 Clinical Study Report, Table 22
Abbreviations: CDR, correct detection rate; CI, confidence interval; EAP, efficacy analysis population; PPV, positive predictive value; PSA, prostate-specific antigen

Demographic subgroup analyses based on age and race were performed. Analysis based on sex could not be performed because only male patients were enrolled in this trial. No conclusions could be made regarding trends in patient-level CDR or region-level PPV due to the predominance of White patients enrolled and the uneven number of patients in each race grouping. There were no significant differences in patient-level CDR or region-level PPV when the data were stratified by age groups <65 or ≥65, and <69 or ≥69 (the median age in this trial population).

Data Quality and Integrity

The inspection and review by the FDA OSI of select clinical investigators, the contract research organization that centrally evaluated flotufolastat F 18 PET imaging results, and select clinical sites did not reveal any GCP deficiencies.

There were no investigators with disclosable financial interests.

Efficacy Results – Secondary and Other Relevant Endpoints

Reader agreement was evaluated for the three central readers and 389 patients in the EPSP. Inter-reader Fleiss κ was 0.41 (95% CI: 0.39-0.43). The three readers agreed on the presence or absence of positive lesions across all five evaluated regions in 118 patients (30% unanimity)

Given the concerning level of inter-reader agreement observed overall, reader agreement was further evaluated by regional subgroup. The Fleiss κ for was 0.40 (95% CI: 0.33-0.46) in the prostate/prostate bed, 0.73 (95% CI: 0.67-0.78) in the pelvic lymph nodes, and 0.62 (95% CI: 0.58-0.65) across the other regions.

Cohen's kappa for intra-reader agreement was reported for the EAP but not EPSP. These values ranged from 0.46-0.73.

Dose/Dose Response

A single dose of 8 mCi (296 MBq) +/- 20% of flotufolastat F 18 was administered to patients in this trial. The mean total decay-corrected administered activity in the FAS/FSP was 8.3 +/- 0.61 mCi (306.2 +/- 22.45 MBq), with a range of 6.2 to 9.6 mCi (230.1 to 355.2 MBq). One of the 391 patients (0.26%) in the FAS received a dose below the lower limit of 6.4 mCi, receiving a dose of 6.2 mCi.

Additional Analyses Conducted on the Individual Trial

An exploratory analysis was performed evaluating the patient-level PPV in the EAP, in which any TP region defined a TP patient regardless of any FP regions. Though one of the pre-defined endpoints of the trial was region-level PPV, there may be a benefit to evaluating patient-level PPV. With a TP lesion in any region automatically defining true positivity at the patient-level without regard to findings in any other region, it is expected that the patient-level PPV would be higher than the region-level PPV. Per the Applicant, in mathematical simulation models, the region-level PPV will always be lower than the patient-level PPV when there are three regions,

unless all patients have a TP in all three regions. The patient-level PPV was 55.5%-71.5% depending on the reader, approximately 6-11% higher than the region-level PPV. However, even if the same prespecified threshold of 62.5% were to be applied to the patient-level PPV, it would still not exceed this.

Table 45. Patient-Level PPV (EAP)

Diagnostic Performance Measure	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366
TP	198/357 (55.5%)	188/263 (71.5%)	189/321 (58.9%)	208/321 (64.8%)
FP	159/357 (44.5%)	75/263 (28.5%)	132/321 (41.1%)	113/321 (35.2%)
PPV	55.5%	71.5%	58.9%	64.8%
95% CI	50.1, 60.7	65.6, 76.9	53.3, 64.3	59.3, 70.0

Source: BED-PSMA-302 Clinical Study Report, Table 27
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PPV, positive predictive value; TP, true positive

An analysis was performed to assess the number of patients with negative baseline conventional imaging who were found to have TP lesions, in other words the number of patients who were upstaged by the flotufolastat F 18 PET, stratified by prior treatment. A total of 250 patients had negative baseline conventional imaging. In patients with prior RP, 3.5%-8% of the patients had lesions detected in the prostate bed that were not detected by conventional imaging, while 17.9%-21.4% of patients had lesions detected in the pelvic lymph nodes and 21.4%-25.9% had lesions detected in other areas (essentially distant metastatic sites). In patients treated with prior RT, 39.1%-41.3% had lesions detected in the prostate region that were not detected on conventional imaging, while 6.5% had lesions detected in the pelvic lymph nodes and 19.6%-30.4% had lesions detected elsewhere.

Table 46. Detection of Lesions Missed by Conventional Imaging

Prior Treatment	Region	Statistic	Reader 1 N=250	Reader 2 N=250	Reader 3 N=250	Majority Read N=250
RP (with or without RT)	Prostate bed	n (%)	16/201 (8.0)	7/201 (3.5)	12/201 (6.0)	12/201 (6.0)
		95% CI	4.6, 12.6	1.4, 7.0	3.1, 10.2	3.1, 10.2
	Pelvic lymph nodes	n (%)	41/201 (20.4)	36/201 (17.9)	43/201 (21.4)	42/201 (20.9)
		95% CI	15.1, 26.6	12.9, 23.9	15.9, 27.7	15.5, 27.2
	Other	n (%)	52/201 (25.9)	51/201 (25.4)	43/201 (21.4)	54/201 (26.9)
		95% CI	20.0, 32.5	19.5, 32.0	15.9, 27.7	20.9, 33.6
RT	Prostate bed	n (%)	18/46 (39.1)	19/46 (41.3)	18/46 (39.1)	20/46 (43.5)
		95% CI	25.1, 54.6	27.0, 56.8	25.1, 54.6	28.9, 58.9
	Pelvic lymph nodes	n (%)	3/46 (6.5)	3/46 (6.5)	3/46 (6.5)	3/46 (6.5)
		95% CI	1.4, 17.9	1.4, 17.9	1.4, 17.9	1.4, 17.9
	Other	n (%)	9/46 (19.6)	14/46 (30.4)	9/46 (19.6)	13/46 (28.3)
		95% CI	9.4, 33.9	17.7, 45.8	9.4, 33.9	16.0, 43.5

Source: BED-PSMA-302 Clinical Study Report, Modified Table 28
Abbreviations: CI, confidence interval; PET, positron emission tomography; RP, radical prostatectomy; RT, radiotherapy

The overall detection rate (or PET percent positivity rate) was also assessed in the trial as an exploratory endpoint in the EPSP (all patients with an evaluable PET scan), and ranged from 67.9% to 92% across the three readers, with a value of 82.8% for the majority read. The detection rate was also evaluated in the subgroup of patients with negative baseline imaging in

the EPSP, and ranged from 61.7% to 90.0%, and 78.4% for the majority read. In the EAP, the overall detection rate ranged from 71.9% to 97.5% across the three readers, and 87.7% for the majority read. This is higher than the detection rate reported for other PSMA PET imaging agents in the literature, which range from approximately 60% to 74%. When the detection rate was stratified by baseline PSA level, there was a small trend towards increasing detection rate with PSA, but particularly notable was the high detection rate even at low PSA levels, as seen in Table 47. This was likely driven by a high FP rate in the prostate/prostate bed region, particularly at lower PSA levels, as seen in Table 48.

Table 47. Patient-Level Detection Rate (PET Percent Positivity) Stratified by PSA Level in BED-PSMA-302 by Majority Read (EAP)

(b) (4)

Source: Applicant submitted Draft Labeling Text, Table 7
Abbreviations: CI, confidence interval; EAP, efficacy analysis population; PET, positron emission tomography; PSA, prostate-specific antigen

Table 48. Prostate/Prostate Bed True Positive and False Positive Rates Per Reader in BED-PSMA-302 (EAP)

PSA (ng/mL)	Diagnostic Performance Measure	Reader 1 N=366	Reader 2 N=366	Reader 3 N=366	Majority Read N=366
<0.5	TP	11/ 72 (15.3%)	5/ 9 (55.6%)	4/ 26 (15.4%)	8/ 27 (29.6%)
	FP	61/ 72 (84.7%)	4/ 9 (44.4%)	22/ 26 (84.6%)	19/ 27 (70.4%)
≥0.5 and <1	TP	3/ 38 (7.9%)	1/ 11 (9.1%)	3/ 22 (13.6%)	3/ 19 (15.8%)
	FP	35/ 38 (92.1%)	10/ 11 (90.9%)	19/ 22 (86.4%)	16/ 19 (84.2%)
≥1 and <2	TP	2/ 26 (7.7%)	2/ 8 (25.0%)	3/ 15 (20.0%)	2/ 14 (14.3%)
	FP	24/ 26 (92.3%)	6/ 8 (75.0%)	12/ 15 (80.0%)	12/ 14 (85.7%)
≥2 and <5	TP	25/ 67 (37.3%)	21/ 39 (53.8%)	23/ 45 (51.1%)	25/ 46 (54.3%)
	FP	42/ 67 (62.7%)	18/ 39 (46.2%)	22/ 45 (48.9%)	21/ 46 (45.7%)
≥5 and <10	TP	11/ 28 (39.3%)	10/ 14 (71.4%)	8/ 17 (47.1%)	10/ 18 (55.6%)
	FP	17/ 28 (60.7%)	4/ 14 (28.6%)	9/ 17 (52.9%)	8/ 18 (44.4%)
≥10	TP	9/ 24 (37.5%)	9/ 19 (47.4%)	9/ 22 (40.9%)	9/ 21 (42.9%)
	FP	15/ 24 (62.5%)	10/ 19 (52.6%)	13/ 22 (59.1%)	12/ 21 (57.1%)

Source: Modified Table 14.2.2.3
Abbreviations: EAP, efficacy analysis population; FP, false positive; PET, positron emission tomography; PSA, prostate-specific antigen; TP, true positive

8.1.5. Integrated Assessment of Effectiveness

In total, the Applicant has submitted substantial evidence in support of the effectiveness of flotufolastat F 18 for imaging of PC prior to initial definitive therapy and at recurrence.

Though the BED-PSMA-301 trial failed to meet one of its co-primary endpoints, with all three readers failing to meet the pre-specified statistical threshold of 22.5% for sensitivity when considering the lower bound of the 95% CI, flotufolastat F 18 could still have clinical diagnostic value. The point estimate of specificity was at or above 93% for all three readers, with the lower bound of the 95% CI significantly higher than the pre-specified statistical threshold of 82.5%, and tests with low sensitivity yet high specificity can still have clinical use. From a clinical perspective, imaging with flotufolastat F 18 could have an important impact on treatment decisions, even with low sensitivity and high specificity. Definitive therapies for patients with PC include radical prostatectomy or radiation therapy, both of which entail significant side effects and toxicity. A patient with true pelvic nodal metastasis detected on pre-therapy PET imaging could therefore be spared potentially unnecessary and morbid treatment, while a patient with a pelvic nodal metastasis missed on PET imaging would undergo definitive therapy as if PET imaging were never performed at all. Other PSMA PET agents that are used in clinical practice also have low sensitivity and high specificity.

As noted in the discussion of the results of BED-PSMA-301 above, 60 patients (16.9%) in the FAS/FSP or intent-to-image population were excluded from the primary analysis population. A total of 31 of these 60 patients (51.7%) had positive pelvic lymph nodes identified on the flotufolastat F 18 PET scan, whereas the PET positivity rate in the EAP ranged from 7.8%-12.5%, indicating that these excluded patients may represent a subgroup with a different disease characteristic. One possible explanation may be that the excluded group had more advanced disease and higher likelihood of true pelvic lymph node metastases. With this explanation, the sensitivity as calculated from analysis of the EAP data could represent a significant underestimation. The tipping point analysis performed by the FDA Statistics team revealed that use of a 20% disease positive imputation rate would result in the sensitivity value exceeding the pre-specified threshold of 22.5% for two of the three readers. Based on the explanation above and with this supportive tipping point, the trial would be successful in demonstrating effectiveness of flotufolastat F 18 in detecting N1 disease using this imputation method. Refer to Section 8.3 Statistical Issues for the full tipping point analyses.

Flotufolastat F 18 may also have clinical utility because flotufolastat F 18 PET was able to upstage 3.7%-5.1% of patients from N0 to N1 and 8%-12.2% of patients from M0 to M1 status when compared to baseline conventional imaging. In other words, flotufolastat F 18 PET imaging identified lesions in these patients that may have been missed on standard conventional imaging and could therefore have altered treatment.

Though not a primary endpoint of the trial, the PPV is important to consider since a test with a PPV that is higher than prevalence can add diagnostic value. For a given population, the pre-test probability of a particular patient having pelvic nodal lymph node metastases is equal to the prevalence of positive lymph nodes in the population. Since the PPV of a test provides the probability that a person who tests positive has the disease, a PPV that is higher than prevalence indicates that the test can identify those with positive lymph nodes more accurately than using a prevalence estimate. The PPV for lymph node metastasis ranged from 56.8%-69.6% in the trial. The percent of patients with histopathologic positivity provides an estimate of the prevalence of pelvic lymph node metastases in the trial population; in this trial the

histopathologic positivity rate was 23.6%. According to the literature, approximately 5% of unfavorable intermediate-risk patients, 17-23% of patients of high-risk patients, and 47% of very high-risk patients have pelvic lymph nodes metastases (Rud, et al., 2022) (Kuperus, J. M.; Tobert, C. M.; Semerjian, A. M.; Qi, J.; Lane, B. R.; Michigan Urological Surgery Improvement Collaborative, 2022) (Reichard, et al., 2021). Given the mixed population of the three risk groups in this trial, the observed percent histopathologic positivity rate and the predicted prevalence of pelvic lymph node metastases according to the literature are fairly consistent. Therefore, since the PPV results in BED-PSMA-301 were significantly higher than the prevalence of pelvic lymph node metastases in the trial population, and a comparable prevalence is expected in the population of intended clinical use, the flotufolastat F 18 PET scan has added diagnostic benefit.

The BED-PSMA-302 trial failed to meet one of its co-primary endpoints as well, with all three readers failing to meet the pre-specified statistical threshold of 62.5% for region-level PPV when considering the lower bound of the 95% CI. A major weakness of the BED-PSMA-302 trial was the use of a composite reference standard, which may have contributed to lowering PPV values. Histopathology is considered the gold-standard for SoT determination, but because biopsy of every PET positive lesion was considered unfeasible and unethical, a composite reference standard was established. SoT could be longitudinal imaging with confirmatory imaging being performed up to 90 days after the PET scan, limiting a change in the size of a lesion as indicative of the presence of disease given the relatively short timeframe.

The overreliance on imaging for SoT determination in BED-PSMA-302, with only 69 out of the 366 patients in the EAP (18.9%) having histopathology, was a further weakness of the trial. Analysis by availability of histopathology as SoT suggested performance may have been higher if more patients had histopathology for SoT determination, although potential selection bias for obtaining histopathology data must be also considered.

For patients with only imaging for SoT determination (n=297), only 40.1% had a ^{18}F-fluciclovine scan, which may have more readily detected recurrent disease than the other conventional imaging modalities consisting of bone scan, CT, or MRI. In addition, 73 patients (19.9%) in the EAP had imaging at only one timepoint, which further eroded the reliability of using imaging for SoT in the trial. Analysis of the data using the PP population, which excluded these 73 patients with only one imaging timepoint for SoT determination, revealed endpoint values that were slightly higher than when they were included in the analysis. See Section 8.3 Statistical Issues for imputation approaches for these patients with only one imaging timepoint for SoT determination.

Though patient-level PPV was not a primary endpoint of the trial, it is useful to evaluate here in the BCR setting as in the initial diagnosis setting in BED-PSMA-301, since a test provides additional diagnostic information in the group of patients who test positive if the PPV is higher than prevalence of disease. It is difficult to assess the true prevalence of recurrent disease in the BCR population, because the FN rate in the study cannot be determined since PET negative lesions were not assessed by biopsy or imaging. One possible estimate of the prevalence of recurrent disease is to assume it is comparable to the CDR of other approved PSMA PET imaging agents, which ranged from 47% to 54%. If the true prevalence of recurrent disease in

the population studied is presumed to be between 47% and 54%, then flotufolastat F 18 appeared to add diagnostic value in the subgroup of patients who tested positive since the patient-level PPV was higher than this prevalence value.

The patient-level CDR of flotufolastat F 18 in BED-PSMA-302 indicates usefulness of the drug since 48.3% to 50.9% of biochemically recurrent patients who received flotufolastat F 18 PET (i.e., EPSP population) had at least one lesion correctly identified (i.e., TP). Flotufolastat F 18 PET was further able to identify a recurrent lesion in 6%-27% (depending on prostate/prostate bed, pelvic lymph node, or other region) of patients with a prior prostatectomy and 7%-44% (depending on region) of patients with prior radiation therapy who did not have any lesions identified by conventional imaging. Only 21.9% of the patients in BED-PSMA-302 had recurrent disease identified on baseline conventional imaging whereas 51.4%-54.1% of patients across readers had a SoT-verified recurrence identified by flotufolastat F 18 PET.

A higher than expected detection rate for flotufolastat F 18 was seen in BED-PSMA-302 with an overall value of 87.7% for the majority read in the EAP; detection rates were particularly high at lower baseline PSA levels, with a detection rate of 73% for the majority read in patients with PSA values <0.5 and 81% in patients with PSA values ≥0.5 and <1. These values are not consistent with other approved PSMA PET imaging agents and may be related to the low level of inter-reader agreement observed in BED-PSMA-302, particularly in the prostate/prostate bed region. To mitigate the associated risk of image misinterpretation and false positives in patients with suspected prostate cancer recurrence, the review team and Applicant agreed that the strengthened Warning and Precaution language excerpted below.

> Risk of Image Misinterpretation
>
> Image interpretation errors can occur with Posluma PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of Posluma for imaging metastatic pelvic lymph nodes in patients prior to initial definitive therapy seems to be affected by serum PSA levels and risk grouping [See Clinical Studies (14.1)]. The performance of Posluma for imaging patients with biochemical evidence of recurrence of prostate cancer seems to be affected by serum PSA levels [See Clinical Studies (14.2)]. Flotufolastat F 18 uptake is not specific for prostate cancer and may occur in other types of cancer, in non-malignant processes, and in normal tissues. Clinical correlation, which may include histopathological evaluation, is recommended.
>
> Risk of Image Misinterpretation in Patients with Suspected Prostate Cancer Recurrence
>
> The interpretation of Posluma PET may differ depending on imaging readers, particularly in the prostate/prostate bed region [see Clinical Studies (14.2)]. Because of the associated risk of false positive interpretation, consider multidisciplinary consultation and histopathological confirmation when clinical decision-making hinges on flotufolastat F18 uptake only in the prostate/prostate bed region or only on uptake interpreted as borderline.

Even though the PC populations studied in BED-PSMA-301 and BED-PSMA-302 represented two distinct stages in the natural history of the disease, the trials are considered supportive of one

another since the underlying mechanism for identifying metastatic disease in these two populations is the same. Though only a secondary endpoint, BED-PSMA-301 did demonstrate the ability of flotufolastat F 18 to detect extrapelvic, distant metastatic disease in patients prior to initial definitive therapy against a composite reference standard in a fashion similar to that of BED-PSMA-302 in patients with biochemical recurrence.

Overall, the Applicant does appear to have submitted sufficient evidence for approval in the form of two mutually supportive, adequate and well-controlled trials that demonstrate the effectiveness of flotufolastat F 18 in the setting of PC before definitive treatment and in the setting of recurrent disease.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data pertaining to safety were collected in BED-PSMA-301 and BED-PSMA-302, as well as one phase 1 study, BED-PSMA-101, consisting of 6 healthy volunteers and 10 patients with prostate cancer. Laboratory and EKG data were obtained from BED-PSMA-101 and BED-PSMA-301 alone since this safety information was not captured in BED-PSMA-302. Urinalysis was performed in BED-PSMA-101. Safety data from the retrospective chart review study, BED-PSMA-403, was submitted as supportive material.

No safety review issues were identified during drug development.

8.2.2. Review of the Safety Database

Overall Exposure

Safety data were pooled for BED-PSMA-301 and BED-PSMA-302. Such pooling is reasonable since both trials enrolled only patients with PC, administered the same dose of flotufolastat F 18, had sufficient follow-up, and used the NCI CTCAE v.5 grading system for AEs. BED-PSMA-101 data were not pooled in the safety analysis given that it included a mix of healthy volunteers (including three females) and PC patients, had a shorter follow-up period of 30 days, and used a different grading scale for AEs (did not use the NCI CTCAE v.5 grading system, but simply graded AEs as mild, moderate, or severe). This pooling strategy was presented in the Integrated Summary of Safety Statistical Analysis Plan v.1.0 dated 1/12/2022 and was agreed upon by the Applicant and FDA.

A total of 747 patients were included in the pooled safety data set, comprising 356 patients from the FSP in BED-PSMA-301 and 391 patients from the FSP in BED-PSMA-302. Patients in the FSP of both studies included those who received any amount of flotufolastat F 18. A single dose of flotufolastat F 18 was administered to each patient, and the mean administered activity in the pooled population was 8.29 mCi (306.6 MBq).

Most patients in this pooled safety population were White, as expected since the two trials included predominantly White patients. However, we are unaware of any data to suggest a difference in incidence or severity of AEs based on race.

Table 49: Baseline Characteristics of the Pooled Safety Population

Characteristic	Parameter/Category	BED-PSMA-301 N=356	BED-PSMA-302 N=391	BED-PSMA-301/ BED-PSMA-302 Pooled N=747
Age [years]	n	356	391	747
	Mean (SD)	64.9 (6.98)	68.3 (7.92)	66.7 (7.67)
	Median	65.0	69.0	67.0
	Range	46, 83	43, 86	43, 86
Age category [n (%)]	<65 years	163 (45.8)	121 (30.9)	284 (38.0)
	≥65 years	193 (54.2)	270 (69.1)	463 (62.0)
Race [n (%)]	Black or African American	30 (8.4)	61 (15.6)	91 (12.2)
	White	289 (81.2)	295 (75.4)	584 (78.2)
	Other[1]	4 (1.1)	14 (3.6)	18 (2.4)
	Not Reported	33 (9.3)	21 (5.4)	54 (7.2)
Ethnicity [n (%)]	Hispanic or Latino	17 (4.8)	18 (4.6)	35 (4.7)
	Not Hispanic or Latino	311 (87.4)	342 (87.5)	653 (87.4)
	Not reported	28 (7.9)	31 (7.9)	59 (7.9)
Total administered activity (mCi)	Mean ± SD	8.29 +/- 0.62	8.27 +/- 0.61	8.29 +/- 0.61
	Median (range)	8.3 (5.76, 10.76)	8.28 (6.21, 9.59)	8.3 (5.76, 10.76)

Source: Summary of Clinical Safety, Modified and Integrated Table 3 and Table 4, with FDA Clinical Reviewer conversion of Administered Activity from MBq to mCi
[1] Other includes: American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, and Other
Abbreviations: SD, standard deviation

Adequacy of the Safety Database

The safety database appears adequate considering patient demographics, exposure, and duration of follow-up.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity and submission quality were identified that could have an effect on the safety review.

Categorization of Adverse Events

In BED-PSMA-301, AEs were captured from time of signing of informed consent to the last day of study follow-up, specifically on Visit 1 during screening, on Visit 2 on the day of flotufolastat F 18 administration (Day 1), during the follow-up visit 1-3 days after flotufolastat F 18 injection on Visit 3, and at time of RP and PLND or other planned treatment or biopsy/imaging of suspected M1 lesions up to Day 60. Severity of AEs were graded using the NCI CTCAE v.5, and causality was assessed by both the investigator and the Applicant, with AEs categorized as

either definitely, probably, possibly, or unrelated to flotufolastat F 18. Criteria not covered by CTCAE were graded as mild, moderate, severe, life-threatening, or death. TEAEs were defined as AEs that started or worsened in severity on or after administration of flotufolastat F 18 and on or before Day 4. Verbatim AE terms were coded using MedDRA v.23.0.

In BED-PSMA-302, AEs were also recorded from time of signing of informed consent to the last day of study follow-up, specifically on Visit 1 during screening, on Visit 2 on the day of flotufolastat F 18 administration (Day 1), during the follow-up that occurred up to Day 7, and at time of biopsy of lesions suspicious for recurrence by Day 60 or at time of confirmatory imaging up to Day 90. The severity of the AEs was graded as per BED-PSMA-301. TEAEs were defined as AEs that started or worsened in severity on or after administration of flotufolastat F 18 and on or before Day 7. Verbatim AE terms were coded using MedDRA v.23.0 as well.

For the pooled integrated summary of safety, TEAEs were defined as AEs that started or worsened in severity on or after the date and time of flotufolastat F 18 administration, and on or before 7 days after the date and time of flotufolastat F 18 injection.

Routine Clinical Tests

In BED-PSMA-301, vital signs (temperature, blood pressure, heart rate, and respiration rate) were obtained at screening as well as before and after flotufolastat F 18 PET imaging. Clinical laboratory evaluations (hematology, chemistry, coagulation) and a 12-lead EKG were obtained before flotufolastat F 18 PET imaging on Day 1, and at the safety follow-up on Day 2-4.

In BED-PSMA-302, only vital signs were obtained at screening as well as before and after flotufolastat F 18 PET imaging. Laboratory data and EKGs were not acquired.

More intensive and extensive safety assessments were performed in the BED-PSMA-101 trial. Vital signs were taken at screening, at 11 different time points before and after flotufolastat F 18 administration ranging from -120 minutes to +250 minutes (-120 to -5, -5, +2, +5, +10, +15, +30, +60, +90, +180 and +250 minutes), and at the 24-hour follow-up visit on Day 2 for the healthy volunteers. For the patients with PC, vital signs were also taken at screening and at follow-up, but at 10 different time points on the day of flotufolastat F 18 administration (-120 to -5, -5, +5, +10, +15, +30, +45, +120, +180 and +240 minutes). Laboratory assessments were performed at screening, at four time points before and after flotufolastat F 18 administration ranging from -120 minutes to +250 minutes (-120 to -5, +90, +180 and +250 minutes) for healthy volunteers and at four different time points (-120 to -5, +45, +180 and +240 minutes) for patients with PC, and at the 24-hour follow-up visit. Urinalysis was obtained at screening and at two time points on the day of flotufolastat F 18 administration (-120 to -5 and +250 minutes for healthy volunteers, and -120 to -5 and +240 minutes for PC patients). 12-lead EKG results were obtained at screening, at five different time points before and after flotufolastat F 18 administration ranging from -120 minutes to +250 minutes (-120 to -5, -5, +90, +180 and +250 minutes) for healthy volunteers and at six different time points (-120 to -5, -5, +45, +120, +180 and +240 minutes) for patients with PC, and at the 24-hour follow-up visit; continuous EKG monitoring was performed on lead II from -5 to 250 minutes on the day of flotufolastat F 18 administration for healthy volunteers and from -5 to 240 minutes for patients with PC.

Overall, the clinical testing performed across the three prospective trials appears adequate to assess the safety profile of flotufolastat F 18 in patients with PC. Acquiring laboratory data and EKG results in the BED-PSMA-301 portion of the pooled safety population is sufficient given there were 356 patients in this group, supporting safety data from BED-PSMA-101, and the low chance of any significant impact of the drug on these laboratory values given the microdose mass of the drug to be administered (maximum mass dose <100 μg) and the single administration.

8.2.4. Safety Results

Deaths

There were two deaths reported in BED-PSMA-302.

One patient experienced a TEAE (MedDRA PT: sudden death [grade 5]) leading to death on Day 3, two days after flotufolastat F 18 administration, that was considered as possibly related to the IMP by the investigator but not related to the IMP by the Applicant. The patient was a 73-year-old White male with BCR of PC, hypertension, and chronic kidney disease who went for a 4-mile run the morning of his death, and afterwards complained of dizziness and chest pain. He had breakfast, rested, and then went to lay by the pool and was found unresponsive later that day. Given his symptoms of dizziness and chest pain that occurred shortly after significant exertion, an acute cardiac or cardiopulmonary event are reasonable causes of his death. Since the drug has no known pharmacological activity and the patient had a medical history with risk factors for sudden death from a cardiovascular event or pulmonary embolism, the Applicant's conclusion that this TEAE is unrelated to flotufolastat F 18 is reasonable.

A second patient experienced two AEs (MedDRA PTs: interstitial lung disease and pulmonary fibrosis [grade 5]) on Day 15 that led to death on Day 35. The patient was a 69-year-old White male with a history of PC, interstitial lung disease, pulmonary fibrosis, chronic respiratory failure, coronary artery disease, and hypertension. The AEs were attributed to progression of the patient's underlying interstitial lung disease and pulmonary fibrosis by the investigator and the Applicant. The Applicant's determination that these AEs were not related to flotufolastat F 18 administration is reasonable given the lack of a temporal relationship and the patient's baseline lung disease.

No deaths were reported in BED-PSMA-101 or BED-PSMA-301.

Serious Adverse Events

Two treatment-emergent SAEs were reported in two (0.3%) patients in the pooled safety population. Both patients were enrolled in BED-PSMA-302. One treatment-emergent SAE, sudden death, was discussed above in the section regarding deaths. The second treatment-emergent SAE involved pulmonary embolism on Day 7 in a 70-year-old male with recurrent PC, high cholesterol, and hypothyroidism. None of the treatment-emergent SAE were considered to be related to flotufolastat F 18 by the Applicant. Review of the narrative summaries was performed, and the determinations of relatedness by the Applicant appear appropriate.

Two patients experienced a treatment-emergent SAE in BED-PSMA-101, urinary retention in one (56-year-old white male who had prostatectomy and urinary retention after catheter removal post-surgery) and neutropenic fever in another (73-year-old white male with multiple co-morbidities including gastric cancer, chemotherapy use at time of event, and history of sepsis). Both were considered to be unrelated to flotufolastat F 18, which is reasonable.

Table 50. Serious Treatment-Emergent Adverse Events

			BED-PSMA-301/ BED-PSMA-302 Pooled	BED-PSMA-101	
MedDRA SOC MedDRA PT	BED-PSMA-301 N=356	BED-PSMA-302 N=391	N=747	Healthy Volunteers N=6	Patients With Prostate Cancer N=10
	Number (%) Patients				
At least one treatment-emergent SAE	0	2 (0.5)	2 (0.3)	0	2 (20)
Infections and Infestations	0	0	0	0	1 (10)
Neutropenic infection	0	0	0	0	1 (10)
Renal and Urinary Disorders	0	0	0	0	1 (10)
Urinary retention	0	0	0	0	1 (10)
General Disorders and Administration Site Conditions	0	1 (0.3)	1 (0.1)	0	0
Sudden death	0	1 (0.3)	1 (0.1)	0	0
Respiratory, Thoracic, and Mediastinal Disorders	0	1 (0.3)	1 (0.1)	0	0
Pulmonary embolism	0	1 (0.3)	1 (0.1)	0	0

Source: Summary of Clinical Safety, Table 12
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class

Three patients experienced five non-treatment-emergent SAEs in BED-PSMA-301. These were classified as non-treatment-emergent since they occurred outside the pre-defined window for a TEAE as defined in the protocol, which was after the time of flotufolastat F 18 administration until and including Day 4. One patient experienced aortic aneurysm and carotid artery disease (diagnosed on the flotufolastat F 18 PET/CT), one patient had carotid artery stenosis (identified during cardiology assessment before IMP administration) and acute myocardial infarction (baseline general arteriosclerosis), and one patient experienced a pneumothorax (related to a lung biopsy). None of these SAEs were considered related to flotufolastat F 18, and all resolved. The narrative summaries were reviewed and these conclusions are reasonable.

Four patients experienced 10 non-treatment-emergent SAE in BED-PSMA-302. These were classified as non-treatment emergent since they occurred outside the pre-defined window for a TEAE as defined in the protocol, which was after the time of flotufolastat F 18 administration until and including Day 7. One patient experienced hypotension, lactic acidosis, and presyncope (patient receiving radiation for prostate cancer), one experienced respiratory failure, interstitial lung disease, and pulmonary fibrosis (described above in section detailing deaths), one patient experienced dyspnea, acute kidney injury, and hypokalemia (related to diarrheal episode), and one patient experienced an intra-abdominal hematoma (related to a CT-guided retroperitoneal lymph node biopsy). None of the SAEs were considered related to flotufolastat F 18, and all

resolved except interstitial lung disease and pulmonary fibrosis that led to death as described in the section detailing deaths. The narrative summaries were reviewed and these conclusions are reasonable.

Dropouts and/or Discontinuations Due to Adverse Effects

One patient in BED-PSMA-301 was discontinued for a reported AE (medication error) that was actually not a true AE, but rather a protocol deviation related to administration of an IV contrast agent on the same day as flotufolastat F 18 administration. The patient in the BED-PSMA-302 trial who experienced a TEAE of sudden death also was considered as a discontinuation.

Significant Adverse Events

No significant adverse events noted other than the SAEs above.

Treatment Emergent Adverse Events and Adverse Reactions

66 TEAEs were reported in 56 patients (7.5%) of the 747 patients in the pooled safety data set, inclusive of SAEs. TEAEs occurring in two or more patients are listed in Table 51. The most frequently reported TEAEs were hypertension, headache, diarrhea, nausea, injection site pain, injection site reaction, and anxiety. A total of 49 (74.2%) of the 66 TEAEs were rated as grade 1 in severity. Five TEAEs occurring in five patients were rated grade 3 (aortic aneurysm, hypertension, and pulmonary embolism) and one TEAE in one patient was rated grade 4 (hyperkalemia).

Table 51. Summary of Treatment-Emergent Adverse Events Reported by ≥2 Patients

MedDRA SOC MedDRA PT	BED-PSMA-301 N=356	BED-PSMA-302 N=391	BED-PSMA-301/ BED-PSMA-302 Pooled N=747
	Number (%) Patients		
At least one TEAE	28 (7.9)	28 (7.2)	56 (7.5)
Vascular disorders	4 (1.1)	8 (2.0)	12 (1.6)
Hypertension	2 (0.6)	7 (1.8)	9 (1.2)
Nervous system disorders	6 (1.7)	4 (1.0)	10 (1.3)
Headache	5 (1.4)	2 (0.5)	7 (0.9)
Gastrointestinal disorders	5 (1.4)	4 (1.0)	9 (1.2)
Diarrhea	1 (0.3)	4 (1.0)	5 (0.7)
Nausea	3 (0.8)	1 (0.3)	4 (0.5)
General disorders and administration site conditions	5 (1.4)	5 (1.3)	10 (1.3)
Injection site pain	3 (0.8)	0	3 (0.4)
Injection site reaction	0	2 (0.5)	2 (0.3)
Psychiatric disorders	2 (0.6)	1 (0.3)	3 (0.4)
Anxiety	1 (0.3)	1 (0.3)	2 (0.3)

Blood and lymphatic system disorders	0	0	0
Anemia	0	0	0

Source: Summary of Clinical Safety, Modified Table 9
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse reaction

A total of 30 TEAEs in 25 patients were assessed as related to flotufolastat F 18 administration by the investigators (of note, the TEAE of sudden death in BED-PSMA-302 was originally assessed by the investigator to be related to the IMP, but determined to be unrelated by the Applicant, as detailed in the section on deaths above).

Table 52. Summary of Flotufolastat F 18-Related Treatment-Emergent Adverse Events Assessed as Related to Flotufolastat F 18 Administration by the Investigators

MedDRA SOC MedDRA PT	BED-PSMA-301 N=356	BED-PSMA-302 N=391	BED-PSMA-301/ BED-PSMA-302 Pooled N=747
	Number (%) Patients		
At least one IMP-related TEAE	9 (2.5)	16 (4.1)	25 (3.3)
General disorders and administration site conditions	4 (1.1)	5 (1.3)	9 (1.2)
Injection site pain	3 (0.8)	0	3 (0.4)
Injection site reaction	0	2 (0.5)	2 (0.3)
Fatigue	0	1 (0.3)	1 (0.1)
Injection site discomfort	0	1 (0.3)	1 (0.1)
Peripheral swelling	1 (0.3)	0	1 (0.1)
Sudden death	0	1 (0.3)	1 (0.1)
Gastrointestinal disorders	2 (0.6)	4 (1.0)	6 (0.8)
Diarrhea	1 (0.3)	4 (1.0)	5 (0.7)
Nausea	1 (0.3)	1 (0.3)	2 (0.3)
Abdominal pain	0	1 (0.3)	1 (0.1)
Nervous system disorders	1 (0.3)	4 (1.0)	5 (0.7)
Headache	0	2 (0.5)	2 (0.3)
Dizziness	0	1 (0.3)	1 (0.1)
Dysgeusia	1 (0.3)	0	1 (0.1)
Paresthesia	0	1 (0.3)	1 (0.1)
Vascular disorders	1 (0.3)	3 (0.8)	4 (0.5)
Hypertension	1 (0.3)	3 (0.8)	4 (0.5)
Eye disorders	0	1 (0.3)	1 (0.1)
Vision blurred	0	1 (0.3)	1 (0.1)
Metabolism and nutrition disorders	1 (0.3)	0	1 (0.1)
Hyperkalemia	1 (0.3)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.3)	0	1 (0.1)
Arthralgia	1 (0.3)	0	1 (0.1)

Source: Summary of Clinical Safety, Modified Table 11
Abbreviations: IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

The Applicant proposes to list diarrhea, hypertension, and injection site pain in the prescribing information as the most frequently reported adverse reactions related to flotufolastat F 18 exposure. This appears reasonable given the safety data collected across the trials.

Laboratory Findings

As stated previously, of the pooled safety dataset, only patients enrolled in BED-PSMA-301 had laboratory data evaluations. For hematologic assessments, only minor fluctuations were noted in the mean change from baseline to the safety follow-up visit (Day 2 to 4), and <5% of patients had shifts in hematologic laboratory data from normal to low or high levels. No TEAEs related to hematology laboratory tests were reported. For coagulation labs, only minor fluctuations were noted as well in the mean change from baseline to the safety follow-up visit. For activated partial thromboplastin time, 7.9% of patients had a shift from normal to low between baseline and safety follow-up while 1.4% of patients had a shift from normal to high; 1.7% of patients experienced a shift of the prothrombin INR value from normal to high. However, no TEAEs related to coagulation labs were reported. For chemistry laboratory tests, again, only minor fluctuations were noted in the mean change from baseline to the safety follow-up visit. A total of 6.2% of patients had a shift in bicarbonate from normal to low, and 5.6% of patients had a shift in glucose from normal to high. Hyperkalemia that occurred in one patient was the only reported TEAE related to any laboratory parameter as detailed in the TEAE section above.

Vital Signs

For the pooled safety data set, there were only minor fluctuations observed in the mean change in vital sign parameters from baseline to the safety follow-up visit. TEAEs related to blood pressure (hypertension) occurred in two patients in BED-PSMA-301 and seven patients in BED-PSMA-302. In terms of heart rate, 77 (10.3%) patients shifted from a normal heart rate at baseline to a lower heart rate (40 to 59 bpm) at time of post-dosing on Day 1, and 16 (2.1%) patients shifted to a higher heart rate (101 to 130 bpm). Two TEAEs related to an abnormal heart rate were reported, one in BED-PSMA-301 in a patient who had atrial fibrillation on Day 3 (normal heart rate at screening, pre-dose, and post-dose, overall abnormal EKG assessment at baseline and follow-up), and one in BED-PSMA-302 in a patient who had tachycardia on Day 1 (normal heart rate at screening, pre-dose, and post-dose).

Table 53. Heart Rate Shifts from Baseline to Post-Dose on Day 1 in Studies in Pooled Safety Data Set

Baseline Heart Rate (bpm)	Day 1 Post-Dose Result [n (%)]						
	<40	40-59	60-100	101-130	>130	Missing	Total
<40	1 (0.1)	0	0	0	0	0	1 (0.1)
40-59	1 (0.1)	77 (10.3)	22 (2.9)	0	0	1 (0.1)	101 (13.5)
60-100	0	77 (10.3)	512 (68.5)	16 (2.1)	0	9 (1.2)	614 (82.2)
101-130	0	0	13 (1.7)	12 (1.6)	2 (0.3)	0	27 (3.6)
>130	0	0	0	0	0	0	0
Missing	0	0	2 (0.3)	0	0	2 (0.3)	4 (0.5)
Total	2 (0.3)	154 (20.6)	549 (73.5)	28 (3.7)	2 (0.3)	12 (1.6)	747 (100)

Source: Summary of Clinical Safety, Table 14

Electrocardiograms (EKGs)

As stated previously, of the pooled safety dataset, only patients enrolled in BED-PSMA-301 had EKG evaluations. EKGs were interpreted by the investigators and given an overall assessment of normal or abnormal. Only minor fluctuations in the mean change from baseline to the safety follow-up visit for all parameters including heart rate, PR interval, QRS complex, QTc interval, and QT interval were reported. A total of 21 (5.9%) patients had EKGs interpreted to be normal at baseline but abnormal at the safety follow-up. No TEAEs related to EKG parameters were reported. Most patients (81.5%) had normal QTc intervals at baseline, and 76.7% of patients had a normal QTc interval at follow-up. A total of 25 patients had a change in QTc interval from baseline of ≤30 msec, 3 had a change >30 to 60 msec, and one patient had a change >60 msec that resulted in a shift to the >500 msec QTc category.

QT

Since flotufolastat F 18 is administered as a single dose in a microdose range, no thorough QT clinical trials were conducted or necessary.

Immunogenicity

Since flotufolastat F 18 is administered as a single dose in a microdose range, no specific immunogenicity testing was conducted or was necessary.

8.2.5. Analysis of Submission-Specific Safety Issues

There were no submission-specific safety issues noted.

8.2.6. Safety Analyses by Demographic Subgroups

A total of 31/463 (6.7%) of patients aged ≥65 years and 25/284 (8.8%) of patients aged <65 years in the pooled safety data set experienced a TEAE. There was no significant trend towards increasing or decreasing incidence of TEAEs with age. There were similar findings when the ≥75 years group (8/118 [6.8%]) was compared to the <75 years group (48/629 [7.6%]), again with no trend indicating association of incidence of TEAEs with age. Since only male patients were enrolled in these trials involving prostate cancer, no analysis of the safety data by gender could be performed. Given the relatively small number of TEAEs reported across the two studies and the predominance of White subjects, no conclusions regarding trends in TEAEs between racial groups could be made.

An analysis of the safety data based on dose by weight was also performed by the Applicant. The median dose by weight administered in the pooled safety data population was 0.0935 mCi/kg (3.461 MBq/kg). The incidence of TEAEs in patients who received less than or equal to the median dose by weight was 30/371 (8.1%) and the incidence in patients who received more that the median dose was 26/370 (7.0%). Therefore, no trend in the incidence of TEAEs as related to the dose by weight was seen.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not needed and were therefore not performed. All radiopharmaceuticals carry a low risk of causing a malignancy that is dose-dependent. See Section 6 for information on the radiation dosimetry of flotufolastat F 18.

Human Reproduction and Pregnancy

Flotufolastat F 18 is not for use in females.

Pediatrics and Assessment of Effects on Growth

Flotufolastat F 18 is not for use in pediatric patients. An agreed initial pediatric study plan letter dated 6/2/2021 documented approval of a waiver to conduct pediatric studies as requested.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Because flotufolastat F 18 is an imaging agent administered as a single IV bolus injection by trained medical personnel in a controlled setting, there is no expected potential for drug abuse and minimal potential for overdose. There are no reported cases of overdose by the Applicant. In the rare case of an overdose, patients should be hydrated and void frequently to increase elimination of the drug from the body to reduce radiation exposure. Flotufolastat F 18 is administered as a microdose with no known pharmacological activity and any possible repeat administration of the drug occurs at extended intervals; it is therefore not expected to have a potential for withdrawal or rebound.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Flotufolastat F 18 has not been approved in any country so there are no post-marketing data available.

In addition to the prospective studies presented in this review, the Applicant also conducted a retrospective chart review (BED-PSMA-403) of 558 additional patients with known or suspected prostate cancer who were exposed to flotufolastat F 18 at the Technical University of Munich University Hospital as part of standard clinical care. No safety signals were identified and there were no adverse drug reactions.

Expectations on Safety in the Postmarket Setting

There are no significant safety issues anticipated in the postmarket setting.

8.2.9. Integrated Assessment of Safety

Overall, the safety profile of flotufolastat F 18 is benign and the drug appears well-tolerated in the population of intended use. The radiation effective dose from flotufolastat F 18 (4.2 mSv) is similar to other PET oncology imaging agents and is estimated to impart minimal additional stochastic risk in this patient population.

8.3. Statistical Evaluation

BED-PSMA-301

This was a phase 3, prospective, multi-center, single-arm, single-dose, clinical trial to evaluate the safety and diagnostic efficacy of flotufolastat F 18 for imaging of men with unfavorable intermediate-, high-, or very high-risk prostate cancer who are candidates for initial definitive therapy. This section briefly summarizes information needed to perform statistical evaluation. Details of the BED-PSMA-301 trial description can be found in Section 8.1.

Three hundred and fifty-six newly diagnosed PC patients who elected to undergo radical prostatectomy (RP) and regional pelvic lymph node dissection (PLND) were enrolled at 31 sites in USA, Finland, Germany and Netherlands and received 8 mCi (296 MBq) ±20% of ^{18}F-flotufolastat F 18 intravenous injection. Among them, 296 subjects were scanned with flotufolastat F 18 PET and underwent RP and PLND, constituting the efficacy analysis population (EAP) used for the primary efficacy analysis. PET scans were anonymized, randomized, and read by three independent central PET readers who received specific training on flotufolastat F 18 PET scans and were blinded to all patient information. The standard of truth (SoT) consisted of histopathology of pelvic lymph nodes (PLNs) surgically removed during RP and PLND.

A left or right hemipelvis with at least one flotufolastat F 18 PET-positive PLN and one positive lymph node (LN) as determined by histopathology was deemed a true positive region, as shown in Table 54.

Table 54. Hemipelvis Region (Left or Right) Categorization – BED-PSMA-301

Category	At Least 1 Pathology-Positive LN in the Region	No Pathology-Positive LN in the Region
At least 1 PET-positive LN in the region	True positive	False positive
No PET-positive LN in the region	False negative	True negative

Abbreviations: LN, lymph node; PET, positron emission tomography

A patient with at least one true positive region was classified as a true positive subject. A patient who had no true positive regions was classified according to the following translation of region-level results to patient-level categorization shown in Table 55.

Table 55. Translation of Region-Level to Patient-Level Results in Patients with No True Positive Regions

Patient-Level Categorization	At Least 1 True Negative Region	At Least 1 False Negative Region	At Least 1 False Positive Region
True negative	Yes	No	No
False negative	Yes	Yes	No
False negative	No	Yes	No
False positive	Yes	No	Yes
False positive	No	No	Yes
False negative	No	Yes	Yes

The co-primary efficacy endpoints of patient-level sensitivity and specificity of flotufolastat F 18 PET in detecting N1 (regional lymph node spread) disease compared to histology of pelvic lymph nodes were evaluated for statistical hypotheses of H_0: sensitivity ≤22.5% and specificity ≤82.5% versus H_1: sensitivity >22.5% and specificity >82.5% by the 1-sided exact binomial test on the EAP. For the study to be considered a success, p-values for both co-primary efficacy endpoints must be statistically significant for at least the same two out of three readers. Subject-level sensitivity and specificity results per reader reported by the Applicant are summarized in Table 25 of Section 8.1.2.

In this study, 60 patients did not have SoT for their PET findings, which will affect the interpretation of the coprimary estimands, i.e., patient-level sensitivity and patient-level specificity. There was no pre-specified imputation method in patients who did not have SoT. To address this issue, Table 56 shows an exploratory tipping point analysis for sensitivity assuming that patients with negative PET findings were disease-negative based on a high negative predictive value (NPV) of flotufolastat F 18 PET. Thus, imputation of SoT was performed in PET-positive patients only. For example, reader 1 had 39 PET-positive reads and 21 PET-negative reads in those 60 patients missing SoT, so the number of disease-positive patients used for calculating sensitivity was 74 (39 × 0.1 plus 70, with 70 being the number of patients positive for pelvic lymph node metastases by histopathology SoT) assuming a disease positive rate of the 39 PET-positive patients is 0.1. To tip the sensitivity results from not meeting the pre-specified threshold to meeting the pre-specified threshold, 10% of 39 PET-positive patients would need to be disease positive for reader 1, 20% of 40 PET-positive patients for reader 2, and 30% of 41 PET-positive patients for reader 3. Given the observed point estimate of sensitivity ranging from 23% to 30% in the EAP and considering that almost half of the 60 patients did not undergo RP and PLND due to M1 findings on flotufolastat F 18 PET, as discussed in Section 8.1.2, such disease positive rates in PET-positive patients would be deemed reasonable.

Table 56. Exploratory Tipping Point Analysis for Sensitivity with Imputation in Flotufolastat F 18 PET-Positive Patients Without SoT

Disease Positive Rate	Reader 1 (39 Positive PET Reads, 21 Negative PET Reads)	Reader 2 (40 Positive PET Reads, 20 Negative PET Reads)	Reader 3 (41 Positive PET Reads, 19 Negative PET Reads)
0%	21 / 70=0.30 (0.20, 0.42)	19 / 70=0.27 (0.17, 0.39)	16 / 70=0.23 (0.14, 0.34)
10%	25 / 74=0.34	23 / 74=0.31	20 / 74=0.27

Disease Positive Rate	Reader 1 (39 Positive PET Reads, 21 Negative PET Reads)	Reader 2 (40 Positive PET Reads, 20 Negative PET Reads)	Reader 3 (41 Positive PET Reads, 19 Negative PET Reads)
	(**0.23**, 0.46)	(0.21, 0.43)	(0.17, 0.39)
20%	29 / 78=0.37 (**0.27**, 0.49)	27 / 78=0.35 (**0.24**, 0.46)	24 / 78=0.31 (0.21, 0.42)
30%	33 / 82=0.40 (**0.30**, 0.52)	31 / 82 =0.38 (**0.27**, 0.49)	28 / 82=0.34 (**0.24**, 0.45)
40%	37 / 86=0.43 (**0.32**, 0.54)	35 / 86=0.41 (**0.30**, 0.52)	32 / 86=0.37 (**0.27**, 0.48)
50%	41 / 90=0.46 (**0.35**, 0.56)	39 / 90=0.43 (**0.33**, 0.54)	37 / 91=0.41 (**0.30**, 0.51)
60%	44 / 93=0.47 (**0.37**, 0.58)	43 / 94=0.46 (**0.35**, 0.56)	41 / 95=0.43 (**0.33**, 0.54)
70%	48 / 97=0.49 (**0.39**, 0.60)	47 / 98=0.48 (**0.38**, 0.58)	45 / 99=0.45 (**0.35**, 0.56)
80%	52 / 101=0.51 (**0.41**, 0.62)	51 / 102=0.50 (**0.40**, 0.60)	49 / 103=0.48 (**0.38**, 0.58)
90%	56 / 105=0.53 (**0.43**, 0.63)	55 / 106=0.52 (**0.42**, 0.62)	53 / 107=0.50 (**0.40**, 0.59)
100%	60 / 109=0.55 (**0.46**, 0.64)	59 / 110=0.54 (**0.44**, 0.63)	57 / 111=0.51 (**0.42**, 0.61)

FDA statistical reviewer analysis. Bolded value indicates a lower bound of the 95% confidence interval is above the 0.225 threshold.
Abbreviations: PET, positron emission tomography; SoT, standard of truth

Table 57 shows an exploratory tipping point analysis for sensitivity in which all 60 patients who were missing SoT were imputed (assuming all those 60 patients are PET-positive). This tipping point analysis was performed based on the intent-to-image population. To tip the sensitivity results from not meeting the pre-specified threshold to meeting the pre-specified threshold, 10% of the 60 patients would need to be disease positive for readers 1 and 2 and 20% for reader 3.

Table 57. Exploratory Tipping Point Analysis for Sensitivity with Imputation in All 60 Patients Without SoT

Disease Positive Rate	Reader 1 (39 Positive PET Reads, 21 Negative PET Reads)	Reader 2 (40 Positive PET Reads, 20 Negative PET Reads)	Reader 3 (41 Positive PET Reads, 19 Negative PET Reads)
0%	21 / 70=0.30 (0.20, 0.42)	19 / 70=0.27 (0.17, 0.39)	16 / 70=0.23 (0.14, 0.34)
10%	27 / 76=0.36 (**0.25**, 0.47)	25 / 76=0.33 (**0.23**, 0.45)	22 /76=0.29 (0.19, 0.40)
20%	33 / 82=0.40 (**0.30**, 0.52)	31 / 82=0.38 (**0.27**, 0.49)	28 / 82=0.34 (**0.24**, 0.45)
30%	39 / 88=0.44 (**0.34**, 0.55)	37 / 88=0.42 (**0.32**, 0.53)	34 / 88=0.39 (**0.28**, 0.50)
40%	45 / 94=0.48 (**0.37**, 0.58)	43 / 94=0.46 (**0.35**, 0.56)	40 / 94=0.43 (**0.32**, 0.53)
50%	51 / 100=0.51 (**0.41**, 0.61)	49 / 100=0.49 (**0.39**, 0.59)	46 / 100=0.46 (**0.36**, 0.56)
60%	57 / 106=0.54 (**0.44**, 0.64)	55 / 106=0.52 (**0.42**, 0.62)	52 / 106=0.49 (**0.39**, 0.59)

Disease Positive Rate	Reader 1 (39 Positive PET Reads, 21 Negative PET Reads)	Reader 2 (40 Positive PET Reads, 20 Negative PET Reads)	Reader 3 (41 Positive PET Reads, 19 Negative PET Reads)
70%	63 / 112=0.56 (**0.47**, 0.66)	61 / 112=0.54 (**0.45**, 0.64)	58 / 112=0.52 (**0.42**, 0.61)
80%	69 / 118=0.58 (**0.49**, 0.67)	67 / 118=0.57 (**0.47**, 0.66)	64 / 118=0.54 (**0.45**, 0.63)
90%	75 / 124=0.60 (**0.51**, 0.69)	73 / 124=0.59 (**0.50**, 0.68)	70 / 124=0.56 (**0.47**, 0.65)
100%	81 / 130=0.62 (**0.53**, 0.71)	79 / 130=0.61 (**0.52**, 0.69)	76 / 130=0.58 (**0.49**, 0.67)

FDA statistical reviewer analysis. Bolded value indicates a lower bound of the 95% confidence interval is above the 0.225 threshold.
Abbreviations: PET, positron emission tomography; SoT, standard of truth

Another exploratory analysis was performed on patient-level positive predictive value (PPV) of flotufolastat F 18 PET by reader and is summarized in Table 58. In a recent survey reported by the US Centers for Disease Control and Prevention, approximately 77% of all prostate cancers in the United States over a 15-year period were localized to the prostate, and 11% had N1 involvement (Siegel, O'Neil, Richards, Dowling, & Weir, 2020). Table 58 shows that patient-level PPV of ^{18}F-rhPSMA-7.3 PET for each reader is greater than 11%.

Table 58. Patient-Level PPV Results – BED-PSMA-301

Statistics	Reader 1	Reader 2	Reader 3
Subject-level PPV	21 / 37=0.57	19 / 33=0.58	16 / 23=0.70
(95% confidence interval)	(0.40, 0.73)	(0.39, 0.75)	(0.47, 0.87)

Abbreviations: PPV, positive predictive value

BED-PSMA-302

This was a phase 3, prospective, multi-center, single-arm, single-dose clinical trial to evaluate the safety and diagnostic efficacy of flotufolastat F 18 PET in men with suspected biochemical recurrence (BCR) of prostate cancer.

Three hundred and eighty-nine patients with a diagnosis of BCR based on elevated serum prostate-specific antigen (PSA) following prior radical prostatectomy or radiation therapy and eligible for potential salvage treatment were enrolled at 28 sites in the USA, Finland, and Netherlands. Patients received 8 mCi (296 MBq) ±20% of [1] flotufolastat F 18 by intravenous injection and underwent flotufolastat PET. PET images were anonymized, randomized, and read by three independent central readers blinded to all patient information. To assess statistical issues associated with the primary efficacy endpoints of patient-level correct detection rate (CDR) and region-level positive predictive value (PPV), we summarize below the SoT steps used for confirmation of positive lesions on flotufolastat F 18 PET.

Step 1

Histological confirmation whenever possible. If flotufolastat F 18 PET scan shows one or more lesions of recurrence in a region, the most accessible and feasible (as judged by the local investigator) lesion in the region was biopsied. If histology was not available or determined non-diagnostic (and re-biopsy not possible), then SoT was confirmed with imaging as described in Steps 2 to 4.

Step 2

Historical and baseline conventional imaging. If historical conventional imaging had been acquired as part of a patient's prostate cancer management prior to acquisition of baseline conventional imaging, then comparison of historical images to baseline images was used to establish SoT.

Step 3

Confirmatory imaging up to 60 days post- flotufolastat F 18 PET. In cases where, in the opinion of the local site investigator, historical conventional imaging was not available or inconclusive for comparison to baseline conventional imaging, confirmatory ^{18}F-rhPSMA-7.3 PET follow-up imaging was acquired.

Step 4

Additional confirmatory imaging. If, in the opinion of the local investigator, Steps 2 or 3 do not allow SoT determination, then a final follow-up flotufolastat F 18 PET confirmatory scan could be obtained up to 90 days post-^{18}F-rhPSMA-7.3 PET.

All conventional and confirmatory imaging scans acquired under Steps 2 to 4 above were read by three central readers different from those readers involved in flotufolastat F 18 PET image interpretation. Annotated PET imaging and a brief summary of clinical information was available to the confirmatory imaging readers (for example, 67-year-old male post-radical prostatectomy with pelvic lymph node dissection and adjuvant pelvic radiation therapy 5 years before; PSA rising to 1.2 ng/mL prior to flotufolastat F 18 PET scan; PSA 9 months).

Of those 389 patients with evaluable PET images, 366 had sufficient data for clear SoT classification of PET-positive regions and constituted the efficacy analysis population (EAP) used for the primary efficacy analysis.

The co-primary efficacy endpoints were 1) the patient-level correct detection rate (CDR) defined as the percentage of patients with at least one true positive lesion (localized correspondence between flotufolastat F 18 PET imaging and SoT) among all EAP patients and 2) the region-level positive predictive value (PPV) defined as the percentage of regions (prostate bed, pelvic, lymph nodes and extra-pelvic sites) with at least one true positive lesion among all PET-positive regions in the EAP patients. In patients with multiple PET-positive lesions in a

specific region, the presence of one true positive lesion determined truth for the region regardless of any coexisting false positive findings in the same region.

Those endpoints were evaluated for the hypotheses of H_0: CDR ≤36.5% versus H_1: CDR >36.5% and H_0: PPV ≤62.5% vs H_1: PPV >62.5% by the 1-sided exact binomial test on the EAP. To adjust the variance estimates according to clustering of regions within a subject, the 1-sided test based on clustered binary data was used to evaluate region-level PPV (Zhou, Obuchowski, & McClish, 2011). For the study to be concluded to be a success, p-values for both co-primary efficacy endpoints must have been statistically significant for at least the same two out of three readers. Patient-level CDR and region-level PPV results per reader are summarized in Section 8.1.4.

The Applicant cited as the major reason for not meeting the pre-specified threshold on region-level PPV the significant challenges in obtaining proof of true-positivity of all PSMA-positive lesions, including the infeasibility of obtaining histology in all lesions / patients and the limited diagnostic performance of conventional imaging in SoT determination, which leads to potential misclassification bias. Table 59 summarizes region-level PPV results, as reported by the Applicant, for the sub-population of patients with histology available as SoT (histology population) and the sub-population of patients with no histology available as SoT in whom conventional imaging used for SoT (no-histology population). The Applicant added majority read results.

Table 59. Region-Level PPV for Histology and No-Histology Populations, Reported by the Applicant

	Population	Reader 1	Reader 2	Reader 3	Majority Read
Region-level PPV (95% confidence interval)	Histology population	67 / 110 0.61 (0.52, 0.70)	69 /103 0.67 (0.58, 0.76)	62 / 99 0.63 (0.54, 0.72)	73 / 102 0.72 (**0.63**, 0.81)
	No-histology population	180 / 425 0.42 (0.38, 0.47)	162 / 280 0.58 (0.52, 0.64)	164 /331 0.50 (0.44, 0.55)	176 / 315 0.56 (0.50, 0.62)

Abbreviations: PPV, positive predictive value, Bolded value indicates a lower bound of the 95% confidence interval is above the 0.625 threshold.

The Applicant claims that the lower bound of the 95% confidence interval of region-level PPV exceeds the pre-specified performance goal of 62.5% for the majority read in the histology population. However, FDA statistical review found that number to be derived in a suboptimal fashion. According to the Applicant's code for majority read count, a PET-positive region is considered true positive if the region is true positive by at least one of three readers, and false positive only if the region is false positive by all three of three readers. Table 60 summarizes region-level PPV results, calculated by the statistics reviewer, using an algorithm in which a PET-positive region is considered true positive only if the region is true positive by at least two of three readers, and false positive otherwise. Using this approach, the lower bound of the 95% confidence interval of region-level PPV is below the pre-specified performance goal of 62.5% for the majority read in the histology population.

Table 60. Region-Level PPV for Histology and No-Histology Populations, Calculated by the FDA Statistics Reviewer

Statistics		Reader 1	Reader 2	Reader 3	Majority Read
Region-level PPV (95% confidence interval)	Histology population	67 / 110=0.61 (0.52, 0.70)	69 / 103=0.67 (0.58, 0.76)	62 / 99=0.63 (0.54, 0.72)	66 / 99=0.67 (**0.56**, 0.76)
	No-histology population	180 / 425=0.42 (0.38, 0.47)	162 / 280=0.58 (0.52, 0.64)	164 / 331=0.50 (0.44, 0.55)	168 / 308=0.55 (0.49, 0.60)

Abbreviations: PPV, positive predictive value

From Table 60, region-level PPV is higher for the histology population than for the no-histology population. Before concluding that the limited diagnostic performance of conventional imaging in SoT determination might be a factor explaining the performance gap, other factors that could impact region-level PPV in the histology population were explored. At region-level, the difference in the distribution of PET-positive regions between histology and no-histology populations was investigated as a possible factor for the performance gap (Table 61). There was a similar distribution in the two populations.

Table 61. Distribution of PET-Positive Regions in Histology and No-Histology Populations*

Region	Histology Population	No-Histology Population
Prostate bed	49 (38%)	216 (31%)
Pelvic lymph nodes	33 (26%)	131 (26%)
Other	47 (36%)	158 (43%)
Total	129 (100%)	505 (100%)

*FDA statistical reviewer analysis
Abbreviations: PET, positron emission tomography

At lesion-level, the difference in the distribution of PET-positive lesion size between histology and no-histology populations was investigated as a possible factor for the performance gap (Table 62). There was a similar distribution in the two populations.

Table 62. Distribution of PET-Positive Lesion Size in Histology and No-Histology Populations*

Size	Histology Population	No-Histology Population
Size <5mm	1 (1%)	5 (1%)
5mm ≤ size <10mm	54 (47%)	224 (52%)
Size ≥10 mm	61 (53%)	202 (47%)
Total	116 (100%)	431 (100%)

*FDA statistical reviewer analysis
Abbreviations: PET, positron emission tomography

At patient-level, the difference in the distribution of PSA level of PET-positive patients between the histology and no-histology populations was investigated as a possible factor for the performance gap (Table 63). The histology population had a lower percentage of patients in the PSA <0.5 category than the no-histology population (16% versus 32%), but the two populations has fairly similar distribution in other categories. This difference in the PSA <0.5 category alone does not seem to be a significant factor contributing to the performance gap.

Table 63. Distribution of PSA Level of PET-Positive Patients in Histology and No-Histology Populations*

PSA Level	Histology Population	No-Histology Population
PSA <0.5	11 (16%)	94 (32%)
0.5 ≤ PSA <1.0	10 (14%)	53 (18%)
1.0 ≤ PSA <2.0	12 (17%)	31 (10%)
2.0 ≤ PSA <5.0	20 (29%)	68 (23%)
5.0 ≤ PSA <10.0	8 (12%)	28 (9%)
10.0 ≤ PSA	8 (12%)	23 (8%)
Total	69 (100%)	297 (100%)

*FDA statistical reviewer analysis
Abbreviations: PET, positron emission tomography; PSA, prostate-specific antigen

We next investigate a possible factor of the diagnostic performance of conventional imaging in SoT determination. Assuming the diagnostic performance of conventional imaging would be as accurate as that of histology in determining SoT, Table 64 reports region-level PPV results in the whole population after applying the region-level PPV of the histology population to the no-histology population for reader 1, reader 2, reader 3, and majority read.

Table 64. Region-Level PPV Assuming Conventional Imaging has the Same Diagnostic Power as Histology*

Reader	Region-Level PPV in Histology Population	Subject # in Histology Population	Subject # in No-Histology Population	Region-Level PPV in Whole Population (95% CI)	Results
Reader 1	0.61	110	425	(535 × 0.61) / 535=0.61 (0.57, 0.65)	Fail**
Reader 2	0.67	103	280	(383 × 0.67) / 383=0.67 (0.62, 0.72)	Fail**
Reader 3	0.63	99	331	(430 × 0.63) / 430=0.63 (0.58, 0.68)	Fail**
Majority read	0.67	99	308	(407 × 0.67) / 407=0.67 (0.62, 0.72)	Fail**

*FDA statistical reviewer analysis; ** the lower bound of the 95% CI did not meet the pre-specified threshold of 0.625.
Abbreviations: CI, confidence interval; PPV, positive predictive value

Patient-level PPV is defined by the Applicant as the proportion of patients with at least one true positive region, regardless of any coexisting false positive regions, among patients with at least one PET-positive region. Patient-level PPV may not be as meaningful in the BCR population as in the initial staging population (Study BED-PSMA-301). It is assumed that every BCR patient has cancer somewhere, making the prevalence essentially 100% in the BCR population, although it may be argued that the prevalence of imageable disease is lower. The primary efficacy interest at the patient-level in the BCR setting would be whether PET imaging actually detects disease-positivity, which was evaluated with patient-level correct detection rate, a co-primary efficacy endpoint. Once a disease-positive patient is identified, PET imaging provides useful information regarding the location of cancer, which can be further evaluated with region-level PPV, the other co-primary efficacy endpoint.

Patient-level PPV evaluates whether PET imaging detects disease-positivity in BCR subjects conditioned on the patient being PET-positive. Patient-level PPV is most useful if a subgroup of PET-positive patients is more likely to have metastasis than the prevalence. However, there is

no such subgroup in the BCR population if the prevalence is considered to be essentially 100%. Patient-level PPV may provide no information on the probability that a specific PET-positive lesion is cancerous.

Patient-level positive predictive value (PPV) of flotufolastat F 18 PET per reader reported by the Applicant is summarized in Table 65.

Table 65. Patient-Level PPV

Analysis Population	Reader 1	Reader 2	Reader 3
EAP	198 / 357=0.55 (0.50 0.61)	188 / 263=0.71 (0.66, 0.77)	189 / 321=0.59 (0.53, 0.64)
PP	177 / 283=0.63 (0.57, 0.68)	170 / 228=0.75 (0.68, 0.80)	172 / 264=0.65 (0.59, 0.71)

Source: Table 9 in 2.5 Clinical Overview of the Applicant's document.
Abbreviations: EAP, efficacy analysis population; PP, per protocol; PPV, positive predictive value

In this study, out of 389 patients enrolled and injected with flotufolastat F 18, 366 in the EAP had data for SoT classification of flotufolastat F 18 PET-positive regions. Data show that only one of the remaining 23 patients had flotufolastat F 18 PET-positive findings. Out of 366 patients in the EAP, 78 were excluded from the per-protocol (PP) population due to major protocol deviations: most (73) of those 78 had no histopathology performed within ±60 days of the PET scan and only had conventional imaging performed at a single time point, deviating from the protocol requirement of having longitudinal imaging for SoT assessment.

Since conventional imaging at a single time point is an inferior and inaccurate way to establish SoT for PET findings, an exploratory analysis was performed to evaluate how patient-level PPV in the EAP would be impacted depending on a true positive rate ranging from 0 to 100% in PET-positive patients excluded from the PP population per reader, as shown in Table 66. For example, reader 1 had 74 PET-positive reads in those 78 patients excluded from the PP population, so the number of PET-positive patients used for calculating patient-level PPV was 357 (74 plus 283).

Keeping 62.5% (performance goal applied to region-level PPV) as a performance goal for patient-level PPV, readers 1 and 3 needed to produce 90% and 80% true positive rates, respectively, to meet the patient-level performance goal. Considering the estimated patient-level PPV of 55% (63%) and 59% (65%) for readers 1 and 3 in the EAP (PP) set, 90% and 80% true positive rates seem too high to achieve.

Table 66. Exploratory Analysis Varying a True Positive Rate for Patient-Level PPV Assessment*

True Positive Rate	Reader 1 (74 Positive PET Reads)	Reader 2 (35 Positive PET Reads)	Reader 3 (57 Positive PET Reads)
0%	177/357=0.50 (0.44, 0.55)	170 / 263=0.65 (0.59, 0.70)	172 / 321=0.54 (0.48, 0.59)
10%	184/357=0.52 (0.46, 0.57)	174 / 263=0.66 (0.60, 0.72)	178 / 321=0.55 (0.50, 0.61)
20%	191 / 357=0.54 (0.48, 0.59)	177 / 263=0.67 (0.61, 0.73)	183 / 321=0.57 (0.51, 0.62)
30%	199 / 357=0.56 (0.50, 0.61)	181 / 263=0.69 (0.63, 0.74)	189 / 321=0.59 (0.53, 0.64)
40%	206 / 357=0.58 (0.52, 0.63)	184 / 263=0.70 (0.64, 0.75)	195 / 321=0.61 (0.55, 0.66)
50%	213 / 357=0.60 (0.54, 0.65)	188 / 263=0.71 (0.66, 0.77)	201 / 321=0.63 (0.57, 0.68)
60%	220 / 357=0.62 (0.56, 0.67)	191 / 263=0.73 (0.67, 0.78)	206 / 321=0.64 (0.59, 0.69)
70%	227 / 357=0.64 (0.58, 0.69)	195 / 263=0.74 (0.68, 0.79)	212 / 321=0.66 (0.61, 0.71)
80%	235 / 357=0.66 (0.61, 0.71)	198 / 263=0.75 (0.70, 0.80)	218 / 321=0.68 (0.63, 0.73)
90%	242 / 357=0.68 (0.63, 0.73)	202 / 263=0.77 (0.71, 0.82)	223 / 321=0.69 (0.64, 0.74)
100%	249 / 357=0.70 (0.65 0.74)	205 / 263=0.78 (0.73, 0.83)	229 / 321=0.71 (0.66, 0.76)

*FDA statistical reviewer analysis
Abbreviations: PET, positron emission tomography; PPV, positive predictive value

Another exploratory analysis was performed by imputing PET-positive patients included in the EAP but excluded from the PP population with the probability of being true positive based on patient-level PPV in the PP population adjusted by PSA level, an important clinical factor likely to affect the true positive rate. In Table 67 for reader 1, PET-positive patients excluded from the PP population in a specific PSA level were imputed with the lower bound of the 95% confidence interval of patient-level PPV in the PP population in that PSA level, with the last column reporting the resulting patient-level PPV: [50+83+21+23 + (47 × 0.35) + (19 × 0.66) + (6 × 0.51) +(2 *0.60)] / [50+83+21+23+47+19+6 +2]. Similar analyses for readers 2 and 3 are shown in Table 68 and Table 69, respectively.

Keeping 62.5% as a performance goal for patient-level PPV, only reader 2 achieved the goal, which fails to satisfy the rule for study win.

Table 67. Exploratory Analysis of Patient-Level PPV in EAP by Imputation for Reader 1*

PSA Level	Patient-Level PPV in PP	PET-Positive Patients Excluded From EAP	True Positive Rate	Patient-Level PPV in EAP
PSA<1	50 / 113=0.44 (0.35, 0.54)	47	0.35	
1≤PSA<5	83 / 111=0.75 (0.66, 0.83)	19	0.66	210/357=0.59
5≤PSA<10	21 / 30=0.70 (0.51, 0.85)	6	0.51	(0.54, 0.64)
10≤PSA	23 / 29=0.79 (0.60, 0.92)	2	0.60	

*FDA statistical reviewer analysis, imputation using patient-level PPV in PP by PSA level.
Abbreviations: EAP, efficacy analysis population; PET, positron emission tomography; PP, per protocol; PPV, positive predictive value; PSA, prostate-specific antigen

Table 68. Exploratory Analysis of Patient-Level PPV in EAP by Imputation for Reader 2*

PSA Level	Patient-Level PPV in PP	PET-Positive Patients Excluded From EAP	True Positive Rate	Patient-Level PPV in EAP
PSA<1	44 / 70=0.63 (0.50, 0.74)	14	0.50	
1≤PSA<5	82 / 103=0.80 (0.71, 0.87)	16	0.71	191/263=0.73
5≤PSA<10	20 / 26=0.77 (0.56, 0.91)	3	0.56	(0.67, 0.78)
10≤PSA	24 / 29=0.83 (0.64, 0.94)	2	0.64	

*FDA statistical reviewer analysis, imputation using patient-level PPV in PP by PSA level.
Abbreviations: EAP, efficacy analysis population; PET, positron emission tomography; PP, per protocol; PPV, positive predictive value; PSA, prostate-specific antigen

Table 69. Exploratory Analysis of Patient-Level PPV in EAP by Imputation for Reader 3*

PSA Level	Patient-Level PPV in PP	PET-Positive Patients Excluded From EAP	True Positive Rate	Patient-Level PPV in EAP
PSA<1	48 / 98=0.49 (0.39, 0.59)	33	0.39	
1≤PSA<5	82 / 109=0.75 (0.66, 0.83)	17	0.66	200/321=0.62
5≤PSA<10	20 / 28=0.71 (0.51, 0.87)	5	0.51	(0.57, 0.68)
10≤PSA	22 / 29=0.76 (0.56, 0.90)	2	0.56	

*FDA statistical reviewer analysis, imputation using subject-level PPV in PP by PSA level.
Abbreviations: EAP, efficacy analysis population; PET, positron emission tomography; PP, per protocol; PPV, positive predictive value; PSA, prostate-specific antigen

Summary

BED-PSMA-301

Study BED-PSMA-301 met the pre-specified threshold of 82.5% on specificity by all three readers. However, the study did not meet the pre-specified threshold of 22.5% on sensitivity, one of the co-primary efficacy endpoints. Exploratory tipping point analyses for sensitivity endpoint may be supportive in that sensitivity estimate may be tipped to success under a reasonable disease positive rate in PET-positive patients missing SOT.

Acknowledging that the sensitivity co-primary efficacy endpoint analysis finding was not successful, the clinical review team considers patient-level PPV to be a useful measure. The clinical utility of ^{18}F-rhPSMA-7.3 PET may be demonstrated by patient-level PPV if it is higher than the prevalence of the disease of interest. The clinical team cited literature of approximately 24% prevalence of N1 disease in this population. The primary statistical reviewer cited a recent survey reported by the Centers for Disease Control in the United States in which approximately 77% of all prostate cancers in the United States over a 15-year period were localized to the prostate, and 11% had N1 involvement.

The lower bounds of the 95% confidence interval of patient-level PPV for ^{18}F-rhPSMA-7.3 PET is higher than 24% in all three readers. From such exploration, Study BED-PSMA-301 supports the clinical utility of flotufolastat F 18 PET as measured by patient-level PPV.

BED-PSMA-302

Study BED-PSMA-302 met its co-primary endpoint for patient-level CDR in all three readers. However, Study BED-PSMA-302 did not meet the success criterion for co-primary efficacy endpoint region-level PPV:

- Region-level PPV did not meet the performance goal of 62.5% for reader 1, reader 2 or reader 3 in the whole patient population.
- Region-level PPV did not meet the performance goal of 62.5% for reader 1, reader 2, reader 3 or majority read in the patient population where histology was used for SoT determination.
- Even assuming that the diagnostic performance of conventional imaging would be as accurate as that of histology in determining SoT such that region-level PPV in the no-histology population would be similar as that in the histology population, region-level PPV did not meet the performance goal of 62.5% for reader 1, reader 2, reader 3, or majority read in the whole patient population.

Additionally, the lower bound of the 95% confidence interval for patient-level PPV exceeded 62.5% for only one of the three readers. Assessing the clinical value of region-level and patient-level PPV in the BCR setting is challenging given that meaningful disease prevalence estimates are unclear. As discussed in Section 8.1.5, the clinical review team feels that clinical utility can be supported through the successful CDR endpoint.

8.4. Conclusions and Recommendations

The review team concludes that the benefit of flotufolastat F 18 outweighs risk of the drug and recommends approval of flotufolastat F 18 for PET imaging of men with PC with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated PSA level. The review team also recommends strengthening of prescribing information to warn prescribers and mitigate the risk of misinterpretation for patients with suspected prostate cancer recurrence suggested by the results of BED-PSMA-302.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meetings were held, and no external consultations were requested for this NDA.

10 Pediatrics

PC does not occur in the pediatric population, and therefore pediatric studies cannot be conducted for the proposed indication. On 5/25/2021, the FDA Pediatric Review Committee agreed to grant a full waiver of pediatric studies.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information
The following revisions were recommended in the proposed prescribing information.

- 1 Indications and Usage
  The indications statement was revised to reflect phase 3 trial design and to be consistent with other approved PSMA imaging products (e.g., Pylarify).

  Posluma is indicated for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer
  • with suspected metastasis who are candidates for initial definitive therapy
  • with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level

- 2 Dosage and Administration
  The recommended activity of Posluma is 296 MBq (8 mCi), the same activity used in the clinical trials. The recommended maximum volume is 5 mL not to exceed the maximum mass dose 100 mcg of flotufolastat per patient.

  The following specific imaging acquisition instructions were added from the clinical protocol.

  Scan duration is approximately 20 minutes depending on the number of bed positions and acquisition time per bed position (typically 3 minutes). Adapt imaging techniques according to the equipment used and patient characteristics in order to obtain the best image quality possible.

- 5 Warnings and Precautions
  A warning for variability among readers in patients with suspected recurrent prostate cancer was added based on the inter-reader Fleiss κ analysis and multidisciplinary consultation and histopathological confirmation were recommended as a mitigation.

  <u>Risk of Image Misinterpretation in Patients with Suspected Prostate Cancer Recurrence</u>
  The interpretation of Posluma PET may differ depending on image readers particularly in the prostate/prostate bed region [see Clinical Studies (14.2)].

Because of the associated risk of false positive interpretation, consider multidisciplinary consultation and histopathological confirmation when clinical decision-making hinges on flotufolastat F 18 uptake only in the prostate/prostate bed or only on uptake interpreted as borderline.

- 6 Adverse Reactions
  Adverse Reactions (≥ 0.4%) reported in two phase 3 studies (301 and 302) were used for the common adverse reaction table: Diarrhea (0.7%), blood pressure increase (0.5%), and injection site pain (0.4%).

- 14 Clinical Studies
  Patient-level pelvic lymph node detection was included as a primary endpoint in patients with suspected metastatic prostate cancer who are candidates for initial definitive therapy. Additional secondary analysis results for M1 detection were added in this patient population.

  (b) (4)

  Additional results including detection rate by serum PSA level and Fleiss κ analysis for reader agreement were added.

  Refer to the approved labeling for the recommended text.

- Established Name and Drug Identification in Labeling
  The active ingredient of Posluma is flotufolastat F 18 gallium (USAN KL-32). However, the active moiety (i.e., flotufolastat F 18) was also named by USAN (USAN KL-31). The CMC review team originally recommended using the name of the active ingredient for the established name, but the Applicant proposed using only the active moiety name to avoid the gallium being misunderstood as radioactive.

  In fact, gallium contained in all other radioactive diagnostic agents is radioactive: e.g., gallium Ga 68 gozetotide, gallium Ga 68 dotatoc, and gallium Ga 68 dotatate. Furthermore, gallium Ga 68 gozetotide is also used for PET imaging of PSMA in patients with prostate cancer. To avoid confusion with this drug, the review team agreed to the established name of flotufolastat F 18 for Posluma (without gallium).

  In addition, the name of the active moiety was used throughout the labeling in reference to the drug component for consistency (e.g., Warnings and Precautions) except where the name of the active ingredient is required (i.e., 11 Description) and 3 Dosage Forms and Strengths and 16 How Supplied/Storage and Handling to indicate the basis of the amount of radioactivity as flotufolastat F 18 gallium.

12 Risk Evaluation and Mitigation Strategies (REMS)

Risk evaluation and mitigation strategies (REMS) are not needed for flotufolastat F 18.

13 Postmarketing Requirements and Commitment

No postmarketing requirements (PMRs) or postmarketing commitments (PMCs) are recommended for this NDA.

14 Clinical Division Director (or designated signatory authority) Comments

I concur with the assessment of the review team that this application should be approved.

BED-PSMA-301 was an adequate and well-controlled trial in patients prior to initial definitive therapy for unfavorable intermediate and higher risk PC. The trial met its patient-level specificity co-primary endpoint but not its patient-level sensitivity co-primary endpoint for detection of pelvic lymph node metastasis. However, patient-level PPV exceeded the prevalence of pelvic lymph node metastasis in the trial population, and this prevalence is consistent with that reported in the literature and is further expected to be approximated in the population of intended clinical use. Such a finding demonstrates the added diagnostic value of flotufolastat F 18 in this clinical setting. Of note, a similar pattern of low sensitivity and high specificity is common to all currently approved PSMA PET drugs. Although the low sensitivity will decrease the number of patients in whom pelvic lymph node metastasis is identified, patients with false negative results will likely continue with traditional standard of care management. It is also probable that the trial design underestimates diagnostic performance since enrolled patients with extensive disease identified by PET tend to not undergo surgery and resultant truth standard collection, thereby removing potentially easier to diagnose patients from analysis. Imputation analysis of such patients without the surgical truth standard supports this belief. Finally, secondary analyses demonstrated detection of distant metastatic disease outside of the pelvic lymph nodes in a reasonable fraction of patients, including those with negative conventional imaging.

BED-PSMA-302 was an adequate and well-controlled trial in patients with suspected prostate cancer recurrence based on serum PSA levels. The trial met its patient-level CDR co-primary endpoint but not its region-level PPV co-primary endpoint for detection of recurrent prostate cancer lesions. Unlike in BED-PSMA-301, prevalence of disease is unclear in the BCR setting of this trial, making interpretation of PPV results challenging. PPV subgroup analyses suggested that the imaging component of the composite reference standard was suboptimal compared to the infrequently available histopathology results, although selection bias for performing biopsy cannot be excluded. Importantly, flotufolastat F 18 correctly identified at least one recurrent

prostate cancer lesion that was not identified by baseline conventional imaging in a substantial fraction of patients, thereby demonstrating potential clinical utility.

Because of the imperfect diagnostic performance demonstrated in both trials, a warning regarding risk of image misinterpretation error that is shared by currently approved PSMA PET drugs is also included in the prescribing information for flotufolastat F 18. In BED-PSMA-302, detection rate of flotufolastat F 18 was higher than expected, particularly at lower PSA levels and within the prostate/prostate bed where false positive results were relatively frequent and inter-reader agreement was relatively low. Because of this finding, the warning regarding risk of image misinterpretation error in the prescribing information for flotufolastat F 18 has been appropriately strengthened with additional information regarding the risk of variable image interpretation and false positive results specifically in the BCR setting. Clinical correlation, histopathological confirmation, and multidisciplinary consultation are mentioned as approaches to challenging cases in the labeled warning.

As expected for a microdose drug with single or infrequent administration, the safety profile of flotufolastat F 18 demonstrated relatively rare and typically mild adverse reactions. The radiation effective dose is consistent with other oncologic PET imaging and of low anticipated risk.

While the two above described adequate and well-controlled trials demonstrate effectiveness in distinct populations with prostate cancer, they are also mutually supportive of one another. Potential risks related to imaging efficacy are mitigated through labeled warnings. Safety risks are otherwise minor. Overall, a favorable benefit-risk balance has been demonstrated for flotufolastat F 18 for PSMA PET of men with suspected PC metastasis who are candidates for initial definitive therapy and in men with suspected PC recurrence based on elevated serum PSA levels.

15 Office Director (or designated signatory authority) Comments

Although not “first in class” Posluma is a new molecular entity and therefore a subject of an Office level review. I have examined the relevant documents and agree with the Division of Imaging and Radiation Medicine in its assessment that benefits of Posluma outweigh its risks and with its recommendation to approve the drug for indications provided in the agreed upon labeling.

16 Appendices

16.1. References

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16.2. Financial Disclosure

The reliability of the data from the two adequate and well-controlled trials was not affected by any financial considerations.

Covered Clinical Study (Name and/or Number): BED-PSMA-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 258		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): BED-PSMA-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 263		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

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

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

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