CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214793Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(1)
Application Number	214793
Priority or Standard	Priority
Submit Date(s)	September 29, 2020
Received Date(s)	September 29, 2020
PDUFA Goal Date	May 28, 2021
Division/Office	Medical Imaging and Radiation Medicine
Review Completion Date	May 24, 2021
Established/Proper Name	Piflufolastat F 18
Trade Name	PYLARIFY
Pharmacologic Class	Radioactive diagnostic agent
Code name	5020600
Applicant	Progenics Pharmaceuticals, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	9 mCi (333 MBq) intravenous as a bolus intravenous injection
Applicant Proposed Indication/Population	Piflufolastat F 18 Injection is a radioactive diagnostic agent indicated for PET imaging in prostate cancer patients (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	Carcinoma of prostate (disorder)
Regulatory Action	Approval
Indications/Populations	PYLARIFY 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	Carcinoma of prostate (disorder)
Recommended Dosing Regimen	333 MBq (9 mCi) with an acceptable range of 296 MBq to 370 MBq (8 mCi to 10 mCi), administered as a bolus intravenous injection

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADT	androgen deprivation therapy
AE	adverse event
AR	adverse reaction
ASTRO	American Society for Radiation Oncology
BCR	biochemical recurrence
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CDR	correct detection rate
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLR	correct localization rate
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
MRI	magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NPV	negative predictive value
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PET	positron emission tomography
PI	prescribing information
PK	pharmacokinetics
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
SAE	serious adverse event
SAP	statistical analysis plan
SPECT	single photon emission computed tomography
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Piflufolastat F 18, also termed ^{18}F DCFPyL in the scientific literature and PYLARIFY as the proprietary name, (b) (4), positron-emitting radiopharmaceutical that binds to prostate-specific membrane antigen (PSMA), a protein that is overexpressed in most prostate cancers. Piflufolastat F 18 is a new molecular entity. The recommended indications are for positron emission tomography (PET) of PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or who have suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. Piflufolastat F 18 is intended to be administered intravenously at a dose of 9 mCi with an acceptable range of 8 mCi to 10mCi. New drug application (NDA) 214793 for piflufolastat F 18 was submitted under the 505(b)(1) pathway.

1.2. Conclusions on the Substantial Evidence of Effectiveness

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

The first adequate and well-controlled trial evaluated the detection of prostate cancer-bearing pelvic lymph nodes in high-risk patients prior to planned radical prostatectomy and pelvic lymph node dissection. Using histopathology as the reference standard in a patient-level, region-matched analysis, piflufolastat F 18 PET had a sensitivity of 28% to 39%, (lower bound of the 95% confidence interval 17% to 27%), specificity of 95% to 98% (lower bound of the 95% confidence interval 92% to 95%), and positive predictive value (PPV) of 72% to 81% (lower bound of the 95% confidence interval 56% to 62%), depending on the reader. These PPV results exceed the estimated prevalence of pelvic lymph node metastasis in this patient population.

The second adequate and well-controlled trial evaluated the detection of metastatic disease in patients with biochemical recurrence of prostate cancer and negative or equivocal conventional imaging workup. The evaluation of piflufolastat F 18 PET performance in this patient population helped to demonstrate its added value. In the group of patients with composite reference standard information available in a corresponding piflufolastat F 18 PET positive region, patient-level PPV was 85% to 87% (lower bound of the 95% confidence interval 78% to 80%), depending on the reader. In an exploratory analysis in which piflufolastat F 18 PET-positive patients who lacked reference standard information were imputed based on patient-specific factors with estimates of the likelihood that at least one PET positive lesion was reference standard positive,

patient-level PPV was 78% to 81% (lower bound of the 95% confidence interval 71% to 74%), depending on the reader.

The performance of piflufolastat F 18 PET in these two trials demonstrates the clinical usefulness of this imaging test in the studied patient populations. In summary, the Applicant has provided substantial evidence of effectiveness of piflufolastat F 18 PET.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

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

Piflufolastat F 18 is a positron emitting radiopharmaceutical proposed by the Applicant for use with PET imaging in prostate cancer patients (b) (4) . The data submitted in this application from two adequate and well-controlled trials prospectively conducted by the Applicant support approval for imaging evaluation of suspected prostate cancer metastasis in two patient populations, men who are candidates for initial definitive therapy and men with biochemical evidence (based on serum PSA level) of prostate cancer recurrence (hereafter referred to as biochemical recurrence or BCR).

In patients with high-risk prostate cancer who are candidates for prostatectomy, the data submitted show low sensitivity but high specificity of piflufolastat F 18 PET for detection of pelvic lymph node metastases. The data also suggest that the investigational drug performs better in patients with higher risk prostate cancer in this setting. Regardless, it is anticipated that many patients with pelvic lymph node metastases will not be detected by piflufolastat F 18 PET. However, given similar limitations in most available imaging techniques, such false negative results are expected to have no impact on the treatment plan of definitive therapy in affected patients. The potential value of piflufolastat F 18 PET lies in the demonstration that PPV exceeds the expected prevalence of lymph node metastasis in the population of intended use. While a positive PET scan may still need to be confirmed by other means, the results would allow a patient with metastasis to avoid the morbidity of surgery for more appropriate treatment. A positive PET scan might also help target therapy as part of the emerging paradigm of treatment of patients with limited metastases, also referred to as oligometastatic disease.

In patients with biochemical recurrence, the submitted data clearly show favorable performance of piflufolastat F 18 PET. Although traditional evaluation of sensitivity and specificity were precluded by the disease condition and trial design, the PPV results demonstrate that PET positive lesions are likely to be prostate cancer. Additionally, piflufolastat F 18 PET displays good detection of lesions at lower, more clinically meaningful PSA levels. Such imaging qualities have the potential to positively impact patient care in this clinical setting where detection and localization of disease are critical. The diagnostic performance of piflufolastat F 18 in patients with biochemical recurrence also supports the

performance in patients who are candidates for definitive therapy of primary tumor, and vice versa.

For the safety evaluation, 593 patients with prostate cancer received piflufolastat F 18 in the phase 3 studies performed by the Applicant. No deaths or discontinuations due to adverse reaction (AR) were reported from this drug that is administered in microgram doses. One patient with a history of multiple allergies experienced a serious adverse reaction of hypersensitivity. Treatment emergent adverse events were otherwise uncommon and usually mild in intensity. Radiation effective dose from the investigational drug is typical of PET oncology imaging and estimated to impart minimal risk. Risk of misdiagnosis related to false negative and false positive results is applicable to imaging tests in general.

In summary, the benefit of piflufolastat F 18 PET in the indicated patient populations with prostate cancer outweighs the acceptably low risks. Therefore, approval of this application is warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Prostate cancer is the most common cancer in American men and the second most common cause of cancer-related death in this population. • The course of prostate cancer varies widely. While many men will have slow growing cancer that needs no treatment, others will have aggressive disease that leads to pain, debilitation, and death. • The pelvic lymph nodes are typical sites of initial metastasis of prostate cancer. • Proper management of prostate cancer involves assessment of the risk of aggressive disease as well as evaluation of the location and extent of disease.	• Prostate cancer is a serious condition that causes substantial morbidity and mortality. • Imaging of disease can have important impact on patient management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Many imaging techniques have been applied to prostate cancer, including ultrasound, CT, MRI, bone imaging using ^{99m}Tc-medronate or ^{18}F-sodium fluoride, ^{111}In-capromab pendetide SPECT, and PET using ^{11}C-choline, ^{18}F-fluciclovine, or ^{68}Ga PSMA-11. The technique used varies depending on what information is needed. • For patients with newly diagnosed prostate cancer who are at intermediate or higher risk, treatment choice is influenced by whether cancer has spread to regional lymph nodes and more distant sites. Current standard-of-care relies on imaging with ^{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 prostate cancer after prostatectomy has been estimated to occur in up to 30% of men who had no evidence of metastatic disease on initial conventional imaging. While therapeutic methods may be a factor, this recurrence rate suggests that disease outside the prostate gland is missed by conventional imaging techniques in a number of cases. • Prostate cancer recurrence is usually first recognized due to an increase in serum PSA level. Bone scan and CT or MRI are used to locate recurrent disease, because this information might guide optimal therapy. ^{11}C-choline, ^{18}F-fluciclovine, or ^{68}Ga PSMA-11 PET might also be used as they are 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.	• Despite the availability of many different techniques for imaging prostate cancer, there is an unmet need for better diagnostic performance. • 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 approved specifically for imaging of prostate cancer in patients with biochemical recurrence. Lesion detection rates with these agents are limited at the low PSA levels of early recurrence. • ^{68}Ga PSMA-11 has recently been approved for use, but is currently very restricted in geographic availability.
Benefit	• Two adequate and well-controlled prospective trials were conducted by the Applicant and submitted in this NDA.	• There is substantial evidence of effectiveness for piflufolastat F 18.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Trial PyL 2301 (OSPREY) Cohort A enrolled 268 men with high-risk prostate cancer before therapy with radical prostatectomy and pelvic lymph node dissection to determine how effective piflufolastat F 18 is at identifying prostate cancer in the pelvic lymph nodes. In the 252 patients who could be evaluated, the sensitivity was low, but the specificity was high. Positive predictive value (PPV) exceeded the estimated prevalence of pelvic lymph node metastasis in this patient population. Subgroup analyses suggest that the test may perform better in patients with higher risk disease. • Trial PyL 3301 (CONDOR) enrolled 208 men with biochemically recurrent prostate cancer and negative or equivocal results on standard imaging workup to determine the effectiveness of piflufolastat F 18 for identifying sites of recurrent disease. In most of the 99 to 104 (depending on the PET reader) men who had reference standard data for a PET positive region, at least one site seen on the PET was determined to contain prostate cancer recurrence or metastasis. The likelihood that any individual PET positive region was determined to contain prostate cancer recurrence or metastasis was lower, but remained greater than one-half. The PET scan was read as positive in 59% to 66% of imaged patients. Even in those patients with PSA level of 1 ng/mL or less, the PET was read as positive 38% to 47% of the time. While there were weaknesses in the reference standard used in this study, they do not appear to significantly limit interpretation of the results.	• Although the pre-specified sensitivity goal of the PyL 2301 (OSPREY) trial was not met, the observed diagnostic performance supports clinical utility in this patient population. While the low sensitivity means that pelvic nodal disease will be missed in certain patients, a similar limitation applies to current standard-of-care imaging and it is not expected to negatively impact traditional patient management. A positive scan may sometimes need to be confirmed by other means, but could ultimately impact treatment strategy. Because piflufolastat F 18 PET does not rely strictly on size for identification of abnormal lymph nodes, it can be considered a complementary test to CT and MR. • For imaging of disease in patients with biochemical recurrence, piflufolastat F 18 PET met clinically relevant performance goals. The detection rate of piflufolastat F 18 PET is affected by PSA level. However, its performance still suggests meaningful utility in patients with biochemical recurrence of prostate cancer, particularly given its evaluation in patients with negative or equivocal results on standard

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		imaging workup.
Risk and Risk Management	• The studied safety population consisted of 593 men with prostate cancer. • No deaths or study withdrawals related to adverse events occurred. • One patient with a history of multiple allergies had a serious adverse reaction of hypersensitivity. • Adverse events were uncommon and usually mild in intensity. • The radiation effective dose is estimated to be 4.3 mSv for a 10 mCi dose.	• Allergic reaction is often found to occur at low rates with imaging drugs. No unexpected safety concerns are identified. • The radiation effective dose is typical of oncologic PET imaging.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

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

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

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

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

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

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

Piflufolastat F 18 allows PET imaging of prostate cancer through binding to the prostate-specific membrane antigen (PSMA). This molecule, also known as glutamate carboxypeptidase II or folate hydrolase I, is a transmembrane protein with an extracellular enzymatic domain. PSMA is expressed in normal prostate epithelial cells where its function is unknown (Silver et al., 1997; Bostwick et al., 1998). PSMA is also expressed in other normal tissues, particularly the glia of the central nervous system where it is involved in glutaminergic neurotransmission, in the renal proximal tubules, in breast epithelium, and in the gut where it may be involved with folate uptake.

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

The term prostate-specific membrane antigen is somewhat misleading as there are many literature reports of PSMA overexpression in non-prostate malignancies and non-malignant conditions. For many malignancies, this effect may be mediated by expression of PSMA in the neovasculature rather than in malignant cells (Chang et al., 1999). This phenomenon has been reported in several cancers, including non-small cell lung cancer, melanoma, colon cancer, clear cell renal cell carcinoma, and thyroid carcinoma. In certain case series, PSMA expression results in visualization of non-prostate cancers on PET using a related agent, ^{68}Ga-PSMA-11 (Salas Fragomeni et al., 2018). Similarly, benign tumors such as thyroid adenoma and hemangioma (soft tissue and bone) may be visualized by ^{68}Ga-PSMA-11 PET. Normal osteoblasts express PSMA, and this observation may explain case reports of uptake of ^{68}Ga-PSMA-11 in a variety of

benign bone diseases such as Paget disease, fibrous dysplasia, osteoarthritis, and fracture (Hofman et al., 2018) and piflufolastat F 18 uptake in avascular necrosis (Torga et al., 2019).

2.2. Analysis of Current Treatment Options

The use and effectiveness of imaging in patients with prostate cancer varies with the task to be accomplished. Imaging options are summarized in Table 1. Performance estimates listed in this table are not meant for comparative purposes given differences in patient populations and trial designs in which these estimates were obtained. Only ^{111}In-capromab pendetide, ^{11}C-choline, ^{18}F-fluciclovine, and ^{68}Ga-PSMA-11 are approved specifically for prostate cancer imaging. ^{99m}Tc-medronate SPECT and ^{18}F-sodium fluoride PET are used for general imaging of bone lesions. Ultrasound, CT, and MRI are general anatomical imaging techniques. Note that imaging is not currently recommended for prostate cancer screening.

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% (using DWI)	Current best choice for imaging prostate gland
^{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 (b) (4)

Technique	Use in Practice	Efficacy	Comments
^{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% Detection rate 60% (for PSA ≤1.78 ng/mL) Detection rate 96% (for PSA >1.78 ng/mL)	Approved for PET imaging of prostate cancer only in the BCR setting
^{68}Ga-PSMA-11	Initial staging Restaging	Identifying pelvic lymph nodes prior to initial definitive therapy: Sensitivity 47% Specificity 90% Identifying disease after BCR: PPV 91%	Very limited geographic availability of the approved product at this time

Sources: (Leventis et al., 2001; Heck et al., 2014; Poulsen et al., 2014; Mohler et al., 2019), labels for ^{111}In-capromab pendetide, ^{11}C-choline, ^{18}F-fluciclovine, and ^{68}Ga-PSMA-11.
Abbreviations: BCR = biochemical recurrence, BLA = biologics license application, CT = computed tomography, DWI = diffusion weighted imaging, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, PET =positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen, RP = radical prostatectomy, SPECT = single photon emission computed tomography

The diagnostic yield of these tests depends on the likelihood that unknown disease is present in the imaged area, therefore imaging is usually restricted to patients with higher risk disease. This observation also explains some of the variability in the published test performance results; values in Table 1 are from selected studies, or where available from approved labeling. However, it can be summarized that currently available imaging techniques have less than optimal performance for detection of prostate cancer, particularly in clinically meaningful situations where tumor lesions are small in volume.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Piflufolastat F 18 is a new molecular entity and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

On March 9, 2016, FDA received a pre-IND meeting request from the Applicant to discuss their development plan for ^{18}F DCFPyL, which was later termed piflufolastat F 18. The written responses emphasized recommendations for two adequate and well-controlled clinical studies with diagnostic performance of the investigational drug measured against a reference standard. The Applicant subsequently opened IND 129952 with the PyL 2301 (OSPREY) protocol, and a may proceed letter was issued on November 18, 2016.

Multiple Type C meetings were held between the Applicant and FDA during drug development. Notable among these was the meeting of July 20, 2017, where FDA (b) (4) recommended two independent studies, one in pre-prostatectomy patients and the other in biochemically recurrent patients.

On August 3, 2018, a protocol for PyL 3301 (CONDOR) was submitted to the IND.

A Type B end-of-phase meeting was held on May 15, 2019, where the Applicant presented results from PyL 2301 (OSPREY). The Applicant clarified that correspondence of the anatomic location between imaging and pathology was not required for their analysis in Cohort A. The FDA emphasized the importance of colocalization and requested this analysis in the planned NDA submission. The Applicant and FDA agreed that narrative information for patients in PyL 2301 (OSPREY) Cohort A who did not undergo the planned radical prostatectomy and pelvic lymph node dissection would be acceptable for submission to the planned NDA (b) (4)

A pre-NDA meeting was held on February 24, 2020. In addition to discussion of the content and format of the planned NDA submission, the results from PyL 3301 (CONDOR) were presented. FDA indicated their interest in region-level and lesion-level positive predictive value estimation in this study in addition to the planned patient-level analyses. The Applicant agreed to perform these analyses where feasible, but expressed concern that there may not be enough data to do so.

NDA 214793 for piflufolastat F 18 was received by FDA on September 29, 2020, and filed on November 6, 2020. Priority review status was requested and granted.

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

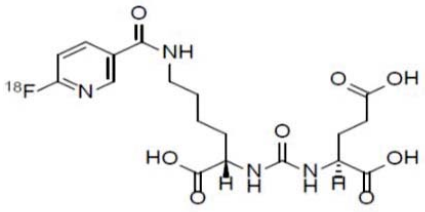
4.1. Office of Scientific Investigations (OSI)

While no specific data quality issues were suspected, because the PyL 2301 (OSPREY) and PyL 3301 (CONDOR) studies provided the primary effectiveness and safety results for regulatory decision making, an Office of Scientific Investigations audit was requested. These inspections were conducted for the Applicant, the two contract research organizations that provided the central PET reads, and two of the largest clinical sites. No significant good clinical practice (GCP) deficiencies were observed for either study, and OSI determined that the data from the inspected sites appeared reliable as reported in the NDA.

4.2. Product Quality

Reference is made to the separate complete product quality review (Integrated Quality Assessment, DARRTS 5/18/21). The drug product, piflufolastat F 18 Injection, contains the active ingredient ,^{18}F-labeled 2-(3-{1-carboxy-5-[(6-[(18)F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (DCFPyL), and the excipients ethanol and 0.9% sodium chloride injection (USP). The drug product is a sterile, clear, pyrogen-free, colorless (b) (4) solution presented in a multiple-dose vial. The synthesis process is (b) (4) The structural formula of piflufolastat F 18 appears in Figure 1 below. Of note, the urea-based PSMA-binding motif of piflufolastat F 18 is shared with the previously approved PET drug, ^{68}Ga-PSMA-11.

Figure 1. Structural formula of piflufolastat F18



The product met all the drug product quality and microbiological quality regulatory specifications. The stability data provided support the proposed 10-hour expiration. The Agency's preapproval inspections of the Applicant's manufacturing facilities (Sofie, Sterling, VA and (b) (4) were completed by (b) (4) and these were found to be adequate. A comparability protocol for addition of manufacturing sites post-approval is approved with the NDA.

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 is approvable from a nonclinical perspective.

Piflufolastat is a glutamate-urea-lysine (EuK)-based inhibitor that binds to and inhibits the N-acetyl-L-aspartyl-L-glutamate (NAAG) peptidase activity of PSMA. PSMA expression in prostate cancer increases with disease progression and is of clinical utility for the detection of primary and metastatic cancer of prostate origin.

The Applicant did not conduct any nonclinical pharmacology studies of piflufolastat to support the submission. Findings from a nonclinical pharmacology study of piflufolastat F 18 that evaluated binding, uptake, and biodistribution in mice (Chen et al., 2011) were supportive, but not essential for approval. Biodistribution and pharmacokinetic data demonstrated greatest uptake of piflufolastat F 18 by PSMA-expressing tissues and rapid clearance by urinary excretion with minimal metabolism. There is clinical pharmacology experience to support specific uptake of piflufolastat F 18 by PSMA expressing tissues, e.g., prostate epithelium, prostate cancer, and metastases of prostate origin (including soft tissue and osseous sites). Safety pharmacology studies were not conducted by the Applicant and are not recommended for microdose radiopharmaceuticals. More importantly, no safety signals have been identified through clinical evaluation of piflufolastat F 18.

The Applicant obtained the right of reference to a nonclinical toxicity study report of piflufolastat F 18 demonstrating safety to support the NDA application. In an extended, single-dose toxicity study in Sprague Dawley rats, no notable findings were reported for piflufolastat at up to 0.5 mg/kg, with a safety factor of 1100-fold based on the intended clinical mass dose of ≤ 4.4 µg. Genotoxicity studies were not conducted and are not recommended for microdose radiopharmaceuticals. Reproductive and developmental toxicity studies were not required for piflufolastat; a waiver was granted based on the proposed single-use indication, target population, and microdose.

In summary, no additional nonclinical studies are necessary to support the safety of piflufolastat F 18 for PET imaging of patients with prostate cancer.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

The Applicant did not conduct pharmacology studies (primary or secondary pharmacology, safety) to support the efficacy or safety of piflufolastat F 18. The Applicant summarized

findings from a nonclinical pharmacology study of piflufolastat F 18 that evaluated PSMA binding, *in vivo* uptake, and biodistribution in a mouse xenograft model of prostate cancer (Chen et al., 2011). The nonclinical findings were supportive of clinical pharmacology findings demonstrating specific uptake in the prostate gland and metastatic lesions of prostate origin with upregulated PSMA expression, as described in Section 6.2.1.

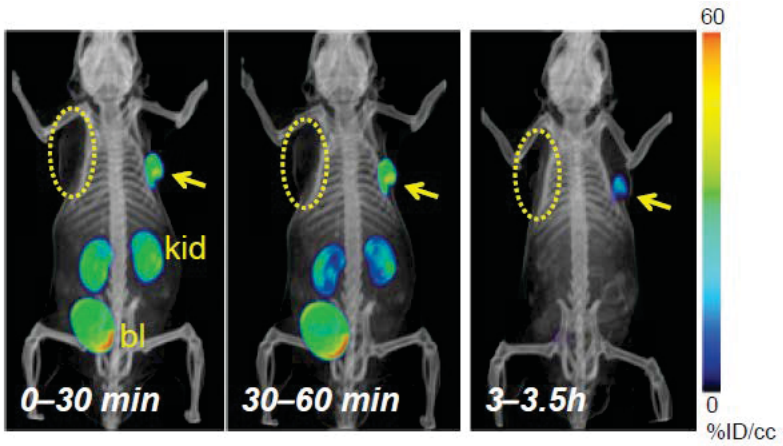
In vitro pharmacology

Piflufolastat is a urea-based ligand for PSMA, a glutamate carboxypeptidase II (also referred to as N-acetyl-L-aspartyl-L-glutamate peptidase I or NAAG peptidase) expressed on the prostate epithelium and overexpressed in prostate cancer. PSMA enzyme activity measured by NAAG peptidase activity was dose-dependently inhibited by piflufolastat with a K_i of 1.1 ± 0.1 nM (Chen et al., 2011).

In vivo pharmacology

The Applicant summarized the findings from a whole-body PET/CT study of piflufolastat F 18 (Chen et al., 2011) performed in a xenograft mouse model of prostate cancer. Nonobese diabetic severe-combined immunodeficient (NOD-SCID) mice were implanted with PSMA positive (PC3 PIP) and PSMA negative (PC3 flu) tumors and piflufolastat F 18 uptake and biodistribution were assessed by PET imaging for up to 4 hours following a single intravenous injection of 0.38 mCi piflufolastat F 18 (Figure 2).

Figure 2. PET-CT volume-rendered composite images representing the time course of radiochemical uptake after administration of piflufolastat F18 in xenograft mice



Source: Figure from Section 2.6.1, page 4 of Applicant Submission

Specific piflufolastat F 18 uptake was observed in PSMA-expressing PC3 PIP tumor (arrow) and was absent in PSMA-negative PC3 flu tumor (dotted oval) by 30 minutes post-dose. Significant uptake was also observed in the kidneys and urinary bladder by 30 minutes that decreased over 3 to 3.5 hours after dosing due to urinary elimination. PSMA-expressing tumor demonstrated

the greatest uptake with a value of 46.7 ± 5.8% injected dose per gram (%ID/g) at 30 minutes with decrease by 10% over 4 hours. The findings from this single study were considered supportive for clinical development of piflufolastat F 18 but not essential for approval. Clinical performance of piflufolastat F 18 in detection of PSMA-expressing tumor was evaluated by use of reference standards that included histopathology results.

5.4. ADME/PK

Studies characterizing absorption, distribution, metabolism, excretion (ADME) or pharmacokinetics (PK) of piflufolastat F 18 administered by the intravenous route were not conducted. The Applicant summarized findings of a single nonclinical study that evaluated uptake and biodistribution in a mouse xenograft model of prostate cancer (Chen et al., 2011). Following intravenous injection of piflufolastat F 18, tissue uptake was rapid with greatest levels found in the kidneys, liver, spleen, and PSMA-positive tumor. Elimination occurred by urinary excretion and was still present in PSMA-positive tumor by 4 hours after dosing. The findings were considered supportive and not essential for approval as there are clinical pharmacology data describing PK/ADME in prostate cancer patients (Refer to Section 6.2.1 Pharmacology and Clinical Pharmacokinetics).

5.5. Toxicology

5.5.1. General Toxicology

The Applicant obtained the right of reference to an extended, single-dose toxicity study in Sprague Dawley rats conducted at the (b) (4) Rats were treated with 0, 0.1, or 0.5 mg/kg piflufolastat by intravenous administration and evaluated for signs of toxicity by mortality, clinical signs, and body weight as well as clinical pathology, macroscopic pathology, and histopathology findings. Main study and recovery animals were euthanized and necropsied on Day 3 and Day 15, respectively. There were no test-article-related findings in rats administered piflufolastat at up to 0.5 mg/kg, the highest dose level tested. The absence of nonclinical findings supports the safety for a single intravenous administration of piflufolastat F 18 based on the proposed clinical mass dose of not more than 4.4 µg (0.073 µg/kg assuming a 60 kg body weight) with an adequate safety factor (1100-fold based on body surface area scaling).

Study title/ number: 14-Day Study to Determine Toxicity of Piflufolastat from a Single Intravenous (IV) Dose in Sprague Dawley Rats / (b) (4)

- Rats received a single intravenous administration of 0, 0.1, or 0.5 mg/kg piflufolastat. No adverse toxicological findings were observed.
- The no-observed-adverse-effect-level was 0.5 mg/kg, the highest dose tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing:	0, 0.1, 0.5 mg/kg; single
Route of administration:	Intravenous
Formulation/Vehicle:	Aqueous solution with 5% dextrose
Species/Strain:	Rat / Sprague Dawley
Number/Sex/Group:	5/sex/group
Age:	7 weeks
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from control

Parameters	Major findings
Mortality	No unscheduled deaths.
Clinical Signs	No drug-related clinical signs noted.
Body Weights	No drug-related effects on body weights or body weight gains.
Hematology	No toxicology significant drug-related findings.
Clinical Chemistry	No toxicology significant drug-related findings.
Gross Pathology	No drug-related macroscopic findings.
Organ Weights	No toxicology significant drug-related findings.
Histopathology Adequate battery: Yes	No drug-related microscopic findings.
Other evaluations	None.

5.5.2. Genetic Toxicology

Genetic toxicology studies were not conducted and are not required for microdose radiopharmaceuticals.

5.5.3. Carcinogenicity

Carcinogenicity studies are not required for microdose radiopharmaceuticals and were not submitted.

5.5.4. Reproductive and Developmental Toxicology

The Applicant requested a waiver for reproductive and developmental toxicology studies. The waiver request was justified because piflufolastat F 18 is a radiopharmaceutical diagnostic drug that will be administered as a single dose of up to 4.4 µg, corresponding to a sub-pharmacologic dose level. Prostate cancer occurs only in men and is more common in older men above 65

years of age at the time of diagnosis. The waiver request was granted based on the proposed single-use indication, mass dose, and intended clinical population.

5.5.5. Other Toxicology Studies

None are needed.

6 Clinical Pharmacology

6.1. Executive Summary

Piflufolastat F 18 binds to the active site of prostate-specific membrane antigen (PSMA) which is overexpressed in prostate cancer cells and is also expressed in some normal organs. Piflufolastat dose-dependently inhibits PSMA enzymatic activity in vitro with a Ki of 1.1 ± 0.1 nM.

The applicant seeks approval of piflufolastat F 18 for use with PET imaging in patients with prostate cancer. The recommended dose of piflufolastat F 18 is a single intravenous bolus injection of 9 mCi (333 MBq) with an acceptable range of 8 mCi to 10 mCi (296-370 MBq).

The recommended dose was selected based on clinical efficacy and safety data of piflufolastat F 18 from two prospective, open-label, multi-center clinical studies: OSPREY (NCT02981368) and CONDOR (NCT03739684). OSPREY evaluated the performance of piflufolastat F 18 PET in two prostate cancer patient populations: patients with high risk prostate cancer planned for surgery as initial definitive therapy (Cohort A), and patients with presumptive radiologic evidence on conventional imaging of recurrent or metastatic prostate cancer that was feasible for biopsy (Cohort B). CONDOR evaluated the performance of piflufolastat F 18 PET in patients with biochemical evidence of prostate cancer recurrence following initial definitive therapy and negative or equivocal baseline imaging. As discussed further in Section 8, piflufolastat F 18 PET results in OSPREY Cohort A and CONDOR from multiple independent, blinded central readers demonstrated adequate imaging efficacy against suitable reference standards.

Patients in both studies received a target dose of 9 mCi (333 MBq) dose of piflufolastat F 18 with mean dose of 9.2 mCi ± 0.7 mCi 1 to 2 hours before undergoing PET/CT imaging. The mean radiation effective dose to the whole body from piflufolastat F 18 was calculated to be 0.0116 mSv/MBq, yielding 3.9 mSv (0.39 rem) for an injected dose of 9 mCi (333 MBq), which is less radiation dose than that of other commonly used tracers for oncologic imaging such as ^{18}F-FDG.

Recommendations

This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness comes from the OSPREY and CONDOR studies.

Review Issue	Recommendations and Comments
General dosing instructions	The proposed dose is 9 mCi (333 MBq) with an acceptable range of 8 mCi to 10 mCi (296-370 MBq) administered as a single intravenous bolus injection.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The effect of hepatic impairment or renal impairment on piflufolastat F 18 pharmacokinetics has not been studied.
Drug-drug interactions	No dedicated drug interaction study was conducted.
Labeling	Generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

6.2. Summary of Clinical Pharmacology Assessment

The pharmacokinetics, distribution, disposition, metabolism and excretion profiles of piflufolastat F 18, as well as normal organ dosimetry, were investigated in a subset of patients with high risk localized prostate cancer who were scheduled to undergo radical prostatectomy with pelvic lymph node dissection in OSPREY (Study PyL2301) following intravenous administration of a 9 mCi dose. Furthermore, the effects of organ (e.g., renal and hepatic) impairment on the diagnostic performance of piflufolastat F 18 and the QTc prolongation potential of piflufolastat F 18 were also assessed in all patients in this study.

Piflufolastat F 18 is a microdose radiopharmaceutical diagnostic agent with the maximum administered mass dose of ≤ 4.4 µg and maximum theoretical instantaneous blood concentration of 1.3 nM. Due to the extremely low chemical mass in the administered dose of piflufolastat F 18, meaningful interactions with metabolizing enzymes, transporters, or ion channels are unlikely to be clinically significant. In addition, piflufolastat F 18 does not undergo metabolism, indicating that blood concentrations of piflufolastat F 18 are not expected to be altered by concomitant CYP P450 inducer or inhibitor drugs.

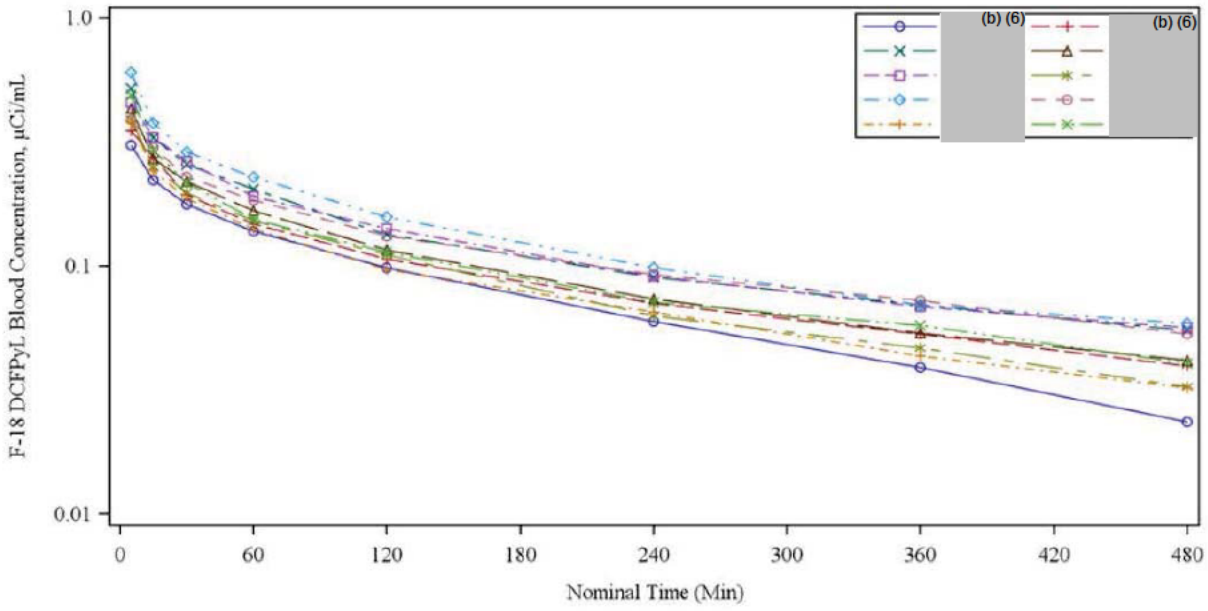
Pharmacology and Clinical Pharmacokinetics:

Piflufolastat F 18 binds to the active site of PSMA which is overexpressed in prostate cancer cells and is expressed normally in certain other organs such as kidneys and parotid glands. Piflufolastat dose-dependently inhibits PSMA enzymatic activity in vitro with a Ki of 1.1 ± 0.1 nM. In mouse xenografts, piflufolastat F 18 is taken up only in PSMA-positive PC3 PIP tumor and not in PSMA-negative PC3 flu tumors, demonstrating that the uptake of piflufolastat F 18 is PSMA-specific (Chen et al., 2011).

The Clinical Pharmacology results from OSPREY (Study PyL2301) are summarized as follows:

• After the intravenous administration of piflufolastat F 18, the blood levels rapidly declined in a biphasic fashion. The half-life of the alpha (distribution) portion of the curve was 0.17 ± 0.044 hours with a beta (elimination) half-life of 3.47 ± 0.490 hour (Figure 3).

Figure 3. Piflufolastat F 18 blood concentrations versus time



Source: Applicant's Summary of Clinical Pharmacology Studies, Module 2.7.2, p.10
Note: Each line represents data from an individual patient

• The plasma-to-blood concentration ratios at any time-point for all patients were between 1.441 and 1.829, indicating piflufolastat F 18 exhibits restricted permeability into RBCs.

• Piflufolastat F 18 was rapidly cleared via the kidney at a rate of 849 ± 237 µCi/hr. By 8 hours post injection, 50.09 ± 7.616 % of the injected dose (ID) (decay-corrected) was present in the urine.

• Amount of injected activity (%ID) remaining in the body by 4 hours post-dose for each patient was derived from the serial PET/CT images. Together with the cumulative urine recovery (0-4 hours), the data establish that urinary excretion is the predominant elimination route of piflufolastat F 18.

• Analysis of plasma samples by high-performance liquid chromatography (HPLC) using a radiometric detector demonstrated that all plasma activity was in the form of unmetabolized radioligand. There were no metabolites detected. All of the radioactivity co-eluted at the same retention time as non-radiolabeled piflufolastat. Urinary excretion is the predominate route of piflufolastat F 18 elimination; the balance of activity not excreted in the urine remained in the body as was demonstrated by imaging techniques (PET/CT). Considering these points, liver function status is not expected to affect piflufolastat F 18 disposition.

• Analysis of sensitivity/specificity versus renal function confirmed that renal function status has no effect on the diagnostic performance of the tracer.

• Piflufolastat F 18 is a microdose radiopharmaceutical diagnostic agent with the maximum administered mass dose of ≤ 4.4 µg and maximum theoretical instantaneous blood concentration of ≤ 1.3 nM. The very low chemical mass in an administered dose of piflufolastat F 18 renders any meaningful interactions with ion channels (e.g., hERG) highly unlikely. In OSPREY, 12-lead ECGs were collected on Day 1, before and after piflufolastat F 18 dosing. There were no clinically relevant changes from baseline to the pre-imaging time point in mean or median QTc values. No patient had ECG results classified as abnormal and clinically significant at baseline or after dosing. The magnitude of changes from baseline in ECG results was small. For QT and QTc intervals, similar percentages of patients had results >450 msec at baseline and after dosing.

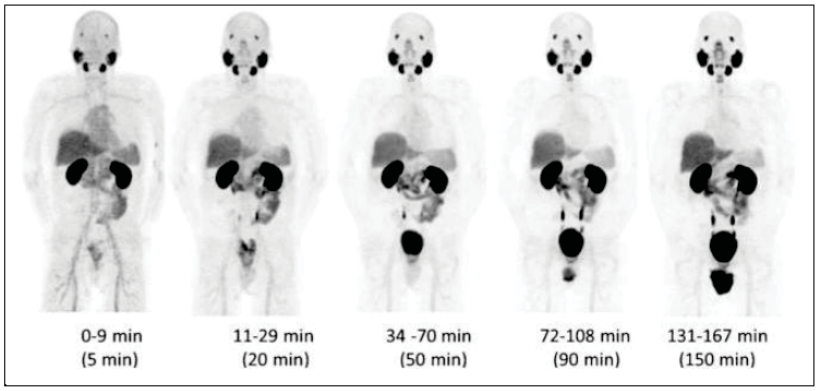
Dosimetry Study:

The Applicant conducted a dosimetry study in patients with prostate cancer. The objective of dosimetry calculations for a diagnostic agent is to estimate the effective dose (*E*). This quantity may be related to a radiation detriment risk.

The data for the calculations were obtained through PET/CT imaging of 18 patients with prostate cancer. The MIRD Committee S-value methodology, as implemented in the OLINDA software, was used to perform the absorbed dose calculations. The S-value methodology provides the absorbed dose to a target tissue as the sum of dose contributions from all of the radioactivity-containing (source) tissues.

Figure 4 depicts a series of piflufolastat F 18 PET images. The images show activity concentration in several of the organs such as liver, kidneys, bladder, parotid glands, and sub-mandibular salivary glands as well as in the lacrimal glands. S-values for these organs are not available. Accordingly, initial dosimetry calculations used surrogate S-values to approximate the electron and photon doses to the eye lens and salivary glands.

Figure 4. Piflufolastat F 18 PET images



Source: Applicant's piflufolastat F 18 Comprehensive Dosimetry Report in Module 5

Time-integrated activity coefficients (TIACs) (i.e., residence times) were obtained by drawing volumes of interest (VOIs) corresponding to each of the organs that could be positively identified on longitudinal PET scans. In most cases the VOI covered the entire organ volume. For cases in which the entire organ volume could not be separated from adjacent structures, a smaller VOI was drawn to estimate the organ concentration. Whole organ TIACs were divided by patient-specific organ masses obtained using CT VOIs and reference organ densities. These were then multiplied by the reference organ masses listed in the OLINDA/EXM software to give scaled organ TIACs appropriate to the reference geometry used in OLINDA/EXM; TIAC concentrations were directly multiplied by the OLINDA/EXM organ masses.

Radiation absorbed dose estimates are shown in Table 2 for organs and tissues of adults from intravenous administration of piflufolastat F 18. The radiation effective dose resulting from administration of 333 MBq (9 mCi) of piflufolastat F 18 to an adult weighing 70 kg is estimated to be 3.9 mSv. Critical organs include kidneys and liver. When PET/CT is performed, exposure to radiation will increase by an amount dependent on the settings used in the CT acquisition.

Table 2. Mean (n=10 patients) radiation absorbed dose for major organs using piflufolastat F 18

Organ/Tissue	Mean absorbed dose per unit administered radioactivity (mGy/MBq ± SD)
Adrenal glands	1.31E-02 ± 1.30E-03
Brain	2.07E-03 ± 3.12E-04
Gallbladder Wall	1.41E-02 ± 1.24E-04
Lower large intestine wall	7.4E-03 ± 9.56E-04
Small Intestine	8.85E-03 ± 9.06E-04
Stomach Wall	9.21E-03 ± 8.41E-04
Upper large intestine wall	9.10E-03 ± 8.94E-04
Heart Wall	1.71E-02 ± 2.21E-04
Kidneys	1.23E-01 ± 4.34E-02
Liver	3.70E-02 ± 5.76E-03
Lungs	1.02E-02 ± 1.61E-03
Muscle	6.86E-03 ± 7.61E-04
Red marrow	7.06E-03 ±7.09E-04
Osteogenic Cells	9.89E-03 ± 1.23E-03
Spleen	2.71E-02 ± 1.15E-02
Urinary bladder wall	7.16 E-03 ± 9.74E-02
EFFECTIVE DOSE	**1.16E-02** ± 2.21E-03 **(mSv/MBq)**

Source: Applicant's piflufolastat F 18 Comprehensive Dosimetry Report in Module 5 (page 8 of 90)

The effective dose estimate of 3.9 mSv for a 9 mCi (333 MBq) injected dose is lower than the effective dose of the routinely used radiopharmaceutical ^{18}F-FDG. The effective dose for ^{18}F-

FDG is about 0.020 mSv/MBq in males and 0.025 mSv/MBq in females, with a 10 mCi (370 MBq) administered dose yielding 7.4 mSv and 9.25 mSv in males and females, respectively. Since the kidneys are the major route of excretion of piflufolastat F 18 and they also contain a high density of PSMA, the kidneys demonstrate the highest radiation absorbed dose for piflufolastat F 18, with an estimate of 41 mGy for a 9 mCi injected dose. Other approved PET imaging drugs often yield critical organ doses of similar magnitude.

6.2.1. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dose of radioactivity to be administered for PET imaging is 9 mCi (333 MBq) administered as a single bolus intravenous injection.

Prior to the first-in-human study with piflufolastat F 18, human dosimetry was extrapolated from a preclinical biodistribution study in xenograft mice (Chen et al., 2011). The urinary bladder wall was projected to be the organ with the highest absorbed dose. The Applicant chose a clinical dose of 9 mCi to limit the estimated radiation-absorbed dose to the urinary bladder wall to approximately 50 mGy.

As discussed above, the radiation effective dose from 9 mCi of piflufolastat F 18 was calculated in humans to be 3.9 mSv, a value comparable to that of other radiotracers used in oncologic imaging. Therefore, a target 9 mCi dosage of piflufolastat F 18 was selected for use in the OSPREY (range 237-393 MBq, 6.4-10.6 mCi) and CONDOR (range 277-410 MBq, 7.5-11.1 mCi) trials. The results of these trials showed acceptable safety and efficacy. Thus, a recommended dose of 9 mCi (333 MBq) with an acceptable range of 8 mCi to 10 mCi (296-370 MBq) is appropriate and reflects variability in dosing in the confirmatory trials.

In both OSPREY and CONDOR, PET/CT imaging was to be initiated 1 to 2 hours after piflufolastat F 18 administration, given evidence of highest uptake and lowest background activity at approximately 1 and 2 hours, respectively. See Table 29 in Section 8.1.4 for the Applicant's analysis of imaging time and performance in CONDOR which led to the labeling recommendation to begin imaging 60 minutes after injection along with the comment that starting image acquisition more than 90 minutes after injection may adversely impact imaging performance.

Therapeutic Individualization

There is no therapeutic individualization proposed.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

In the OSPREY study, 10 patients with high risk localized prostate cancer scheduled to undergo radical prostatectomy with pelvic lymph node dissection (Cohort A) were enrolled in the PK portion of the study. One patient had normal kidney function at screening (eGFR ≥ 90 mL/min/1.73 m^2) while the other nine patients had mild kidney insufficiency (60< eGFR< 90). Each patient received a single intravenous injection of piflufolastat F 18 at a target dose of 9 mCi (333 MBq). An indwelling catheter was inserted into a vein in the opposite arm from the one used for the infusion of piflufolastat F 18. The indwelling catheter was to remain in place throughout the sample collection period. A 4.5 mL baseline blood sample was to be obtained within 48 hours prior to dosing with piflufolastat F 18. In addition, a 4.5 mL blood sample was also to be taken at 5 ± 2 minutes, 15 ± 2 minutes, 30 ± 5 minutes, 1 ± 0.25 hours, 2 ± 0.25 hours, 4 ± 0.25 hours, 6 ± 0.25 hours, and 8 ± 0.25 hours post-dose. Following the administration of piflufolastat F 18, urine was to be collected at time intervals of 0 to 2, 2 to 4, and 4 to 8 hours post-injection. Blood, plasma, and urine samples were analyzed in duplicate for radioactivity using a qualified gamma well counting method. Additionally, urine samples were analyzed for metabolites using a validated high-performance liquid chromatography (HPLC) method. Whole-body PET/CT images were to be acquired in each patient at the following three time points: (1) up to 17 minutes after piflufolastat F 18 injection and prior to voiding, (2) at 1 ± 0.25 hours post-dose, and (3) at 4 ± 0.25 hours post-dose.

The results of this study are summarized in Section 6.2 above.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The imaging and visualization of prostate cancer with adequate piflufolastat F 18 concentrations in tumors and low background radioactivity provides supportive evidence for the efficacy of piflufolastat F 18.

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

The proposed dosing regimen is appropriate for patients with prostate cancer prior to initial definitive therapy and at the time of biochemical recurrence.

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

There is no alternative dosing regimen or management strategy for subpopulations of patients based on intrinsic factors. Piflufolastat F 18 was rapidly cleared via the kidney. By 8 hours after

injection, 50.09 ± 7.616 % of the ID (decay-corrected) was present in the urine. Thus, impairment of renal function could possibly affect the diagnostic performance of piflufolastat F 18. FDA requested that the applicant conduct post-hoc analyses on the effect of renal impairment on specificity and negative predictive value (NPV) in Cohort B of the OSPREY study.

To address FDA's question, the Applicant tabulated the number of patients with either negative biopsy histopathology or negative piflufolastat F 18 imaging according to their renal function: eGFR 30 to < 60 (moderate impairment), eGFR 60 to < 90 (mild impairment), and eGFR >= 90 (normal). However, the number of patients in the eGFR 30 to < 60 group was too small to allow meaningful analysis. Therefore, a post-hoc analysis of specificity and NPV on the eGFR 60 to < 90 (mild impairment) and eGFR $\geq$ 90 (normal) groups was performed (Table 3).

Table 3. Specificity and NPV of piflufolastat F 18 PET by baseline renal function in OSPREY Cohort B patients

Renal Impairment (eGFR)	Reader	Specificity (%)	NPV (%)
Normal (eGFR ≥90)	1	37.5	100
	2	37.5	100
	3	37.5	75.0
Mild (eGFR 60 to <90)	1	23.1	100
	2	30.8	57.1
	3	76.9	83.3

Source: Applicant's Response to IR 1/19/21, Module 1.11.3, SDN 9
Abbreviation: eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2)

In conclusion, within the limitations of the small sample size and reader variability, this post-hoc analysis in OSPREY Cohort B suggests that renal function may not substantially impact specificity and NPV of piflufolastat F 18 PET in this patient cohort.

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

There are no clinically relevant food-drug or drug-drug interactions and no additional management strategy is needed.

Androgen Deprivation Therapy (ADT):
Literature reports have described that androgen deprivation therapies (ADT) can affect PSMA expression in tumors and other organs (Afshar-Oromieh et al., 2018). The data, however, are inconclusive as to whether there is an increase in PSMA expression or not. CONDOR and OSPREY Cohort A both featured an exclusion criterion for concomitant use of ADT.

In OSPREY Cohort B, approximately one-third of the patients (32 out of 93) had concomitant ADT use, which was defined as medications with start dates prior to and ongoing at piflufolastat F18 dosing. The Applicant conducted a post-hoc sub-group analysis of the effect of concomitant

use of ADT on the efficacy of piflufolastat F18 in OSPREY Cohort B patients. The results, as summarized in Table 4 below, show no significant difference in sensitivity or positive predictive value (PPV) in patients who received concomitant ADT compared to patients without ADT use.

Table 4. Effect of concomitant ADT on sensitivity and PPV in OSPREY Cohort B

	OSPREY Cohort B			
	Group (n)	Reader 1	Reader 2	Reader 3
Sensitivity % (95% CI)	No ADT (42-43)	98 (86, 100)	95 (84, 100)	93 (80, 98)
	ADT (28)	100 (86, 100)	96 (81, 100)	93 (76, 99)
PPV % (95% CI)	No ADT (45-54)	76 (64, 87)	77 (66, 89)	87 (73, 94)
	ADT (29-31)	90 (74, 97)	90 (74, 97)	90 (73, 97)

Source: Table 1, Response to IR 1/19/21, Module 1.11.3, SDN 9
Abbreviations: ADT = androgen deprivation therapy, PPV = positive predictive value

While patients with concomitant use of ADT were excluded from CONDOR, 55 patients (26.4%) had prior treatment with ADT. No significant difference was observed on the PPV of piflufolastat F18 in patients previously treated with ADT compared to those without prior treatment (Table 5).

Table 5. Effect of prior ADT on PPV in CONDOR

	CONDOR			
	Group	Reader 1	Reader 2	Reader 3
% PPV (95% CI)	No ADT	82 (73, 91)	84 (75, 93)	83 (74, 92)
	Any ADT	92 (83, 100)	94 (85, 100)	90 (79, 100)
	6-<12 months	100 (45, 100)	100 (29, 100)	100 (29, 100)
	1-<2 years	70 (42, 98)	80 (55, 100)	75 (45, 100)
	≥2 years	100 (100, 100)	100 (100, 100)	95 (85, 100)

Source: Module 5.3.5.2, CONDOR CSR Table 14.2.1.14.
Abbreviation: PPV = positive predictive value

In conclusion, available results showed that there was no clinically significant effect of concomitant or prior use of ADT on the diagnostic performance (sensitivity, PPV) of piflufolastat F18 PET.

Diuretics:
For prostate cancer PET imaging, radioactivity in bladder can interfere with the accurate detection of lesions, particularly in the prostate bed and pelvic lymph nodes. Therefore, voiding the bladder prior to imaging is important. In literature reports for other PSMA-targeting PET drugs, investigators have used diuretics 30 minutes prior to administration of the radiopharmaceuticals to improve lesion detection (Lawhn-Heath et al., 2018).

The Applicant conducted post-hoc analyses to examine the effect of concomitant diuretic use on the diagnostic performance of piflufolastat F18. There were 20/253 (7.9%) evaluable patients in OSPREY Cohort A and 16/93 (17.2%) evaluable patients in OSPREY Cohort B with concomitant diuretic use. The results for OSPREY Cohort A and B showed no clear observable differences in diagnostic performance of piflufolastat F18 for pelvic lymph nodes between the patients who received concomitant diuretics and patients who did not (Table 6). However, these analyses should be interpreted with caution due to the post-hoc nature and small number of patients in certain cohorts.

Table 6. Effect of concomitant diuretics on sensitivity and specificity in OSPREY

	OSPREY		
Group (n)	Reader 1	Reader 2	Reader 3
% Sensitivity (95% CI)	**Cohort A**		
Control (233)	40 (29, 53)	30 (20, 43)	37 (26, 50)
Diuretics (20)	60 (23, 88)	40 (12, 80)	80 (38, 97)
% Specificity (95% CI)	**Cohort A**		
Control (233)	98 (95, 100)	99 (96, 100)	97 (93, 99)
Diuretics (20)	93 (68, 108)	100 (76, 110)	93 (68, 108)
% Sensitivity (95% CI)	**Cohort B**		
Control (78)	98 (93, 101)	95 (93, 101)	92 (93, 101)
Diuretics (16)	91 (67, 104)	100 (70, 104)	91 (69, 104)

Source: Source: Table 1, Response to IR 1/19/21, Module 1.11.3, SDN 9

In conclusion, available data do not suggest that concomitant use of diuretics at the time of dosing significantly impacted the diagnostic performance of piflufolastat F18. The Applicant's clinical trials were not conducted with a required diuretic, therefore we have no recommendation for the use of diuretics.

7 Sources of Clinical Data and Review Strategy

Appears this way on original

7.1. Table of Clinical Studies

Table 7. Listing of clinical trials

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Phase 3 studies to support efficacy and safety							
PyL 2301 (OSPREY) Cohort A	NCT02981368	Prospective, single-arm, open-label	Single 8-10 mCi i.v. dose of piflufolastat F 18	Patient-level sensitivity and specificity for pelvic lymph node metastases by histopathology reference	268	Patients with at least high risk prostate adenocarcinoma who were candidates for prostatectomy	8 U.S. sites, 2 Canadian sites
PyL 3301 (CONDOR)	NCT03739684	Prospective, single-arm, open-label	Single 9 mCi ± 20% i.v. dose of piflufolastat F 18	Patient-level positive predictive value for recurrent prostate cancer by composite reference standard	208	Patients with biochemically recurrent prostate cancer and negative or equivocal conventional imaging	13 U.S. sites, 1 Canadian site
Other studies pertinent to the review of efficacy and safety							
PyL 2301 (OSPREY) Cohort B	NCT02981368	Prospective, single-arm, open-label	Single 8-10 mCi i.v. dose of piflufolastat F 18	Patient-level sensitivity and positive predictive value by histopathology reference	117	Patients with recurrent or metastatic prostate cancer and a finding amenable to biopsy on conventional imaging	8 U.S. sites, 2 Canadian sites
Other studies pertinent to the review of safety							
J17149	NCT03471650	Prospective, single-arm, open-label	Single approximately 9 mCi i.v. dose of piflufolastat F 18	Urinalysis results	9	Patients with elevated PSA who had not yet had a prostate biopsy	1 U.S. site

Source: FDA clinical reviewer.
Abbreviations: i.v. = intravenous, U.S.= United States of America

7.2. Review Strategy

Primary evidence of effectiveness and safety for piflufolastat F 18 PET for imaging of prostate cancer was provided in two prospective trials, PyL 2301 (OSPREY) Cohort A and PyL 3301 (CONDOR). These trials were conducted in two distinct populations, patients with at least high-risk prostate cancer who were candidates for initial definitive therapy with prostatectomy and patients with biochemical recurrence of disease who had negative or equivocal conventional imaging, respectively. PyL 2301 (OSPREY) Cohort B studied patients with findings on conventional imaging that were suspected to represent recurrent or metastatic prostate cancer. This is not a population in which substantial clinical use is expected, however the results were reviewed for supportive purposes.

Analyses performed by the clinical reviewer used SAS Enterprise Guide version 8.1. Two-sided 95% confidence intervals for proportions used the method of Wald without continuity correction, unless the sample size was small (defined as $np < 5$ or $n(1-p) < 5$), in which case Agresti-Coull confidence intervals were reported.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PyL 2301 (OSPREY) Cohort A

Trial Design

PyL 2301 (OSPREY) was a prospective, single-arm, open-label study of piflufolastat F 18 for imaging of PSMA-expressing prostate adenocarcinoma. The study was performed in the United States and Canada. Results obtained from the Canadian participants should be applicable to the United States population. PyL 2301 (OSPREY) enrolled patients into 2 distinct cohorts, A and B. This section applies only to Cohort A; Cohort B is discussed separately in Section 8.1.5.

PyL 2301 (OSPREY) Cohort A included adult males with biopsy-proven prostate adenocarcinoma. Patients were considered to have high risk or very high risk disease by NCCN criteria, version 3.2016. All patients were planning to undergo radical prostatectomy with pelvic lymph node dissection for definitive therapy, and none were to have received androgen deprivation therapy. Patients were to have conventional imaging, including chest CT, abdomen/pelvis CT or MRI, and ^{99m}Tc-MDP or ^{18}F-fluoride bone scan, within 6 weeks prior to administration of the investigational drug, but these scans could be obtained during screening if not already done.

After enrollment, each patient was administered 9 ± 1 mCi piflufolastat F 18 intravenously. As discussed in Section 6 of this review, this dose was chosen based on early phase experiments referenced by the Applicant. One to two hours post injection, PET/CT images were obtained from the mid-thigh to the skull vertex.

A contract research organization, (b) (4) was responsible for collecting and interpreting PET/CT and baseline conventional images. The PET/CT images were centrally evaluated by three independent, blinded radiologists or nuclear medicine physicians. Blinding specifically included local radiology assessments, clinical information, and baseline conventional imaging. Training was required for the readers prior to participation in the study. Each reader evaluated multiple pelvic lymph node regions bilaterally on each PET/CT as positive, negative, or not evaluable. Positive was defined as “uptake greater than background activity and judged by the reader to be consistent with disease”. The baseline conventional images were evaluated by a single blinded central radiologist distinct from the three central piflufolastat F 18 PET readers.

After the PET/CT, patients were to proceed to the scheduled radical prostatectomy and pelvic lymph node dissection. For the pelvic lymph node dissection, surgeons were requested to remove all lymphatic tissue on and between the external iliac vein and the internal iliac vessels bilaterally per standard-of-care minimum template. Additional tissue could be removed along

the external iliac artery, common iliac artery, and common iliac vein at the surgeon's discretion, and tissue from all these areas were to be sent for histopathology analysis along with the minimum template dissection in single specimen containers for each of the left and right sides. Any other dissected nodes, including in the presacral region, were to be sent in separate containers. The extent of dissection was documented. The number of histopathology positive lymph nodes and number of lymph nodes removed were extracted from pathology reports.

Table 8 summarizes the study procedures.

Table 8. PyL 2301 (OSPREY) schedule of events

	Screening / Baseline	**Piflufolastat F 18 Dosing**	**Piflufolastat F 18 Imaging**	**Pre-Surgery Follow-Up**
	Day-30 to Day 1	**Day 1**	**1-2 Hours Post Dosing**	**Within 28 Days Post Dosing**
Cohorts A and B				
Informed Consent & Eligibility	X			
Demographics (date of birth, race, ethnicity, height, weight, BMI)	X			
Medical History	X			
Prior Cancer Medications & Treatments	X			
Clinical Labs (Hematology, Chemistry)	X			X
PSA (Total) & Testosterone	X			
Vital Signs (Blood Pressure, Heart Rate, Temperature, Respiratory Rate)	X	X (pre-dosing)	X (pre-imaging)	X
12-Lead Electrocardiogram (ECG)		X (pre-dosing)	X (pre-imaging)	
Piflufolastat F 18 Administration		X		
Whole Body PET/CT			X	
Adverse Events		X		X
Concomitant Medications	X	X		X

Conventional Imaging (CT or MRI, Bone Scan)	X			
Surgery				X

Source: Table 3 of PyL 2301 (OSPREY) Protocol, amendment 2.

Study Endpoints

The co-primary endpoints were patient-level specificity and sensitivity of piflufolastat F 18 PET/CT for detection of pelvic lymph node prostate cancer metastases against a histopathology reference standard derived from the tissues removed at pelvic lymph node dissection. FDA agreed with these endpoints at a meeting with the Applicant on 11/2/2017.

Current standard-of-care therapy for prostate cancer localized to the prostate gland most often includes observation, radiotherapy, or prostatectomy, with the choice often depending on histologic grade and other factors predictive of aggressiveness. If disease has spread beyond the prostate gland, prostatectomy has traditionally been considered futile, and the substantial morbidity associated with prostatectomy is generally avoided in this situation. However, the potential option of directed therapy of oligometastatic disease is also currently being explored clinically. In either case, management decisions often rely on accurate detection and localization of extraprostatic lesions. Unfortunately, currently approved imaging techniques have limited sensitivity and specificity for detection of pelvic nodal metastases and distant metastatic disease. Thus, there is an unmet need for agents that can detect extraprostatic disease.

Because prostate cancer most often spreads to the pelvic lymph nodes before becoming widely metastatic, and because pelvic nodal dissection is frequently performed along with prostatectomy for staging and prognostic purposes, assessing performance of piflufolastat F 18 PET for detection of pelvic lymph node metastases as an endpoint is both clinically relevant and practical. The main limitation of the endpoint is that extrapelvic metastases are not considered, however, these are less common, and other studies submitted with this application provide relevant information, albeit in different patient populations.

For the central PET reads, each reader assigned a status of positive, negative, or not evaluable to 10 different pelvic lymph node regions:

- Minimum template (left, right)
- External iliac artery (left, right)
- Common iliac vein (left, right)
- Common iliac artery (left, right)
- Presacral
- Other

As discussed above, the minimum template included the lymphatic tissue along the external iliac vein extending to the internal iliac vessels at surgery. A region was considered positive if it

contained at least one PET positive lymph node. The attenuation correction CT could be used to guide lesion localization but CT size or morphology were not criteria for determining whether a lymph node was positive. Separately, lymph node counts were also provided for four pelvic regions (template right, template left, presacral, other pelvic).

For the primary analysis, the overall reference standard status for the pelvic lymph nodes was considered positive if at least one lymph node from the pelvic lymph node dissection contained prostate carcinoma, and negative if lymph nodes were dissected but none were positive. Regions that were non-evaluable on PET were excluded from consideration. The overall PET status of the pelvic lymph nodes was considered positive if there was at least one PET positive region corresponding to a region that was dissected, and negative if none of the dissected regions were PET positive. These data were used to construct a 2x2 table and derive specificity and sensitivity. Note that while the PET results for this analysis were restricted to the regions that were dissected, there was no matching of location between PET positive regions and histopathology positive regions. Also note that presacral lymph nodes were excluded from analysis per protocol Amendment 1. However, only two patients had dissection of the presacral region and the presacral region status would not have changed the patient-level result for these patients.

Patient-level positive predictive value (PPV) of piflufolastat F 18 PET/CT for detection of pelvic lymph node prostate cancer metastases against a histopathology reference standard was an important secondary endpoint. If the study population closely matches the clinical use population, a PPV result greater than the observed rate of histopathology positive pelvic lymph nodes in all trial patients would demonstrate potential clinical utility. Additionally, identification of patients with pelvic lymph node metastases without an unduly large number of false positive results is anticipated to be one important use of piflufolastat F 18 PET in this patient population. The PPV endpoint was derived in the same manner as the primary endpoints.

Other endpoints of special interest include patient-level sensitivity, specificity, and PPV for detection of pelvic lymph node metastases where the PET result and histopathology result were colocalized at the region-level. The Applicant derived these endpoints as a post hoc analysis. Three regions were defined for the analysis, left template, right template, and other, and regional PET status was derived in a similar manner as for the overall pelvis. Each of the three regions was determined to be true positive, false positive, false negative, true negative, or unevaluable. Patients were then categorized twice using the rule that the first matching regional result from each of the following ordered lists defined the patient-level result: TP, FN, FP, TN and TP, FP, FN, TN. For example, using the first list, if a patient had groups that were FP, FP, and TP, the patient would be TP, while if they had groups that were TN, FP, and FN, they would be FN.

Statistical Analysis Plan

Applicant-defined populations of interest include:

- Safety Set: all patients who received any amount of piflufolastat F 18

- Evaluable Set: patients who received piflufolastat F 18, had a prostatectomy or lymphadenectomy, and had a PET image result (positive or negative) and a corresponding histopathology result (positive or negative)
- Per Protocol Set: patients in the Evaluable Set without any major protocol deviations

Primary endpoint analysis was based on the Evaluable Set. Thresholds were set at 0.80 for specificity and 0.40 for sensitivity, against which the lower bound of the 95% confidence interval would be compared. For study success, at least two of the three readers would need to meet the threshold for each endpoint, and if only two readers were successful, they had to be the same two readers for specificity as well as for sensitivity.

Protocol Amendments

The initial PyL 2301 (OSPREY) protocol was dated 7/12/2016. No patients were enrolled under this version of the protocol. Two amendments were made, on 9/16/2016 and on 11/6/2017.

In Amendment 1, presacral pelvic lymph nodes were removed from analysis. A range of 9 ± 1 mCi was specified for the administered dose of piflufolastat F 18. Investigators were instructed to image all patients if safe, rather than to discontinue patients with large extravasations from the study. Adverse event (AE) intensity grading was changed to CTCAE version 4.03 rather than mild, moderate, and severe classification. Numerous other changes were made, largely clarifying or administrative in nature. The Applicant states that 296 patients (cohorts A and B combined) were enrolled under this version of the protocol.

The major changes in Amendment 2 were to the objectives and endpoints to refocus on Cohort A rather than a pooled analysis from cohorts A and B. This protocol version contains primary endpoints for Cohort A only. In addition, the site of disease for which performance of piflufolastat F 18 was to be estimated in Cohort A was changed from prostate gland to pelvic lymph nodes. Sensitivity and specificity threshold goals were modified accordingly. The enrollment target was increased from 290 patients to 377 patients, and the relative proportion of patients in Cohort A was increased. Collection of alternate treatment plan information was added for patients who did not complete the intended surgical procedure. The Applicant states that 89 patients were enrolled under this version of the protocol.

8.1.2. Study Results - PyL 2301 (OSPREY) Cohort A

Compliance with Good Clinical Practices

The Applicant indicated that the study was performed in compliance with good clinical practice (GCP) and with oversight from site IRBs.

Financial Disclosure

The Applicant stated that four investigators at two sites had disclosable financial interests. The potential for bias related to these interests was minimized by the Applicant's use of an independent contract research organization to generate blinded PET reads.

Patient Disposition

A total of 268 patients were enrolled in Cohort A, all of whom received the investigational drug and were members of the Safety Set. There were 16 patients (6% of the Safety Set) that were not evaluable, leaving 252 patients in the Evaluable Set. An additional four patients were withdrawn prior to completion of the study due to investigator decision, but were considered evaluable.

The Applicant provided narratives for 14 of the 16 nonevaluable patients describing the alternate treatment chosen instead of radical prostatectomy with pelvic lymph node dissection. These alternate treatments are summarized in Table 9. Many of these patients went on to have ADT (69%) and/or radiotherapy (44%), and the narrative usually stated that this decision was due to unexpected sites or extent of extraprostatic disease found by the investigational PET.

Table 9. Summary of narratives for nonevaluable patients

Patient	Local PET Result			Alternative Treatment				
	T	N	M	Focal Gland	Radiotherapy	ADT	Chemo	Active Surveillance
(b) (6)		-	-	X				
			+		X	X		
		-	-		X			
			+			X		
		-	-		X	X		
		+				X		
		+	-		X	X		
	-	-	-					X
		+	+			X		
			+			X		
		+	+		X	X		
		+	+		X	X	X	
		+	-		X	X		
			+			X	X	

Source: FDA clinical reviewer analysis, based on PyL 2301 (OSPREY) Patient Narratives.
Abbreviations: - = negative, + = positive, ADT = androgen deprivation therapy, Chemo = chemotherapy, M = extra-pelvic metastasis, N = pelvic lymph nodes, PET = positron emission tomography, T = prostate
** = Patient had positive bone biopsy after the investigational PET.

Protocol Violations/Deviations

The Applicant reported 10 major protocol deviations among six patients in the Evaluable Set (2.4%). Three patients were administered piflufolastat F 18 intended for use in another clinical trial at the institution, and one of these patients was administered a dose of 6.6 mCi, below the intended range of 8-10 mCi. Three patients were unable to complete the radical prostatectomy

but did have the pelvic lymph node dissection. Two patients had received anti-androgen therapy prior to enrollment, which was an exclusion criterion. Another patient did not meet eligibility criteria due to receipt of an unspecified medication about 3 months prior to the PET scan. One patient did not meet the high risk or very high risk inclusion criterion, being categorized as intermediate risk by NCCN criteria.

None of these protocol deviations are expected to have a substantial impact on the primary analysis for this study.

Demographic Characteristics

The demographic features of the patients in the Safety Set are summarized in Table 10. The mean age was 64 years, and the age distribution was nearly even between patients younger than 65 and those 65 years or older. Most patients were white. The proportions of patients of black or Asian race or of Hispanic or Latino ethnicity are mildly lower than the general United States population per the latest Census estimates (black 9% versus 13%, Asian 3% versus 6%, Hispanic 4% versus 19%; https://www.census.gov/quickfacts/fact/table/US/PST045219, accessed 1/15/2021). However, the review team was unable to find data to suggest that the investigational agent will perform less well in non-white patients. There are some published results that suggest PSMA PET could perform better in black South Africans than white South Africans (Sathekge et al., 2018), presumably due to differences in PSMA expression on prostate cancer cells.

Table 10. Demographics for the Safety Set of PyL 2301 (OSPREY) Cohort A

Parameter	Safety Set (n=268) n (%)
Age	
Mean years (SD)	64.0 (6.7)
Median (years)	65.0
Min, max (years)	46, 84
Age Group	
< 65 years	132 (49%)
≥ 65 years	136 (51%)
Race	
White	233 (87%)
Black or African American	23 (9%)
Asian	7 (3%)
Other	2 (<1%)
Unknown/Denied	3 (1%)
Ethnicity	
Hispanic or Latino	11 (4%)
Not Hispanic or Latino	256 (96%)
Missing	1 (<1%)
Region	
United States	204 (76%)
Canada	64 (24%)

Source: PyL 2301 (OSPREY) Clinical Study Report, Table 11 and FDA clinical reviewer (Region).
Abbreviations: max = maximum, min = minimum, n = number of patients, SD = standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Selected baseline characteristics for the patients in the Safety Set are shown in Table 11. The Applicant provided information related to three key factors that contribute to the risk estimates for prostate cancer under the NCCN classification scheme: tumor stage, Gleason score, and PSA level (Mohler et al., 2019). A patient is categorized as high risk or very high risk if he meets any of the following three criteria: T3a or greater tumor stage, total Gleason score of 8 or more, or PSA >20 ng/mL. Note there are other variables that can influence the overall risk classification that are not considered here. Of the analyzed factors, Gleason score was most commonly in the high risk or greater range, seen in 81% of patients. Approximately 28% of patients had tumor stage in the high risk or greater range, and 18% met the PSA threshold.

The majority of patients in the Safety Set (74%) had at least mild renal impairment, defined as eGFR less than 90 mL/min/1.73 m^2, though no patient met the criterion for severe renal impairment of <30 mL/min/1.73 m^2. Because renal impairment will likely be a common comorbidity in prostate cancer patients, and because piflufolastat F 18 is predominantly excreted through the urinary tract, the inclusion of patients with renal impairment is a strength of the study.

All patients had conventional imaging results at baseline, usually collected after enrollment, consisting of either CT or MRI as well as a bone scan performed using ^{99m}Tc-MDP, ^{99m}Tc-HDP, or ^{18}F-NaF. Prior to enrollment, 97% of patients had no evidence of pelvic lymph node metastasis (N0 or Nx) and 99% had no evidence of distant metastasis (M0 or Mx) on available conventional imaging. For the anatomic imaging, CT with contrast was used in the large majority of patients (263/268, 98%) and MRI was used for only three patients. The protocol-defined CT and MR anatomic coverage included the chest, abdomen, and pelvis. Baseline conventional imaging found pelvic lymph nodes suspicious for metastasis in 38% of patients and lesions suspicious for distant metastasis in 17%.

Table 11. Baseline characteristics for the Safety Set of PyL 2301 (OSPREY) Cohort A

Parameter	Safety Set (n=268) n (%)
Tumor Stage Prior to Study Entry	
TX	8 (3%)
T2	7 (3%)
≤T2a	135 (50%)
T2b-T2c	44 (16%)
T3	3 (1%)
T3a	56 (21%)
T3b-T4	15 (6%)
Total Gleason Score	
≤6	3 (1%)
7	49 (18%)
8	120 (45%)

9-10	96 (36%)
PSA	
<10 ng/mL	134 (50%)
10-20 ng/mL	86 (32%)
>20 ng/mL	47 (18%)
Missing	1 (<1%)
eGFR	
≥90 mL/min/1.73 m^2	67 (25%)
60-89 mL/min/1.73 m^2	181 (68%)
30-59 mL/min/1.73 m^2	16 (6%)
Missing	4 (1%)
Baseline Conventional Imaging Status	
Baseline imaging performed	268 (100%)
Baseline imaging positive for pelvic lymph nodes	101 (38%)
Baseline imaging positive for distant metastases	46 (17%)

Source: PyL 2301 (OSPREY) Clinical Study Report, Tables 12 and 13, FDA clinical reviewer analysis (baseline imaging positivity).
Abbreviations: eGFR = estimated glomerular filtration rate, n = number of patients, PSA = prostate-specific antigen, TX = tumor stage undetermined

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites; therefore, drug compliance is not applicable.

As discussed under Patient Disposition and Protocol above, 19 patients from the Safety Set (7%) did not receive the planned surgical treatment, and of these 16 (6%) did not have a pelvic lymph node dissection to allow evaluation of the primary endpoint. The impact of potential bias from the resultant lack of reference standard information is considered low due to the relatively small number of involved patients. In addition, 10 of the 16 patients were managed using non-surgical therapy due to local interpretation of the investigational PET showing evidence of unanticipated or greater than anticipated extraprostatic disease. It is possible that such patients would have easier to detect disease due to larger or more numerous lesions. Thus, bias from exclusion of such patients might be expected to lower the estimated performance of the investigational drug.

Efficacy Results – Primary and Major Secondary Endpoints

The Applicant's primary endpoint results are shown in Table 12. All three readers exceeded the predefined specificity goal of 80%, however, none of them met or exceeded the sensitivity goal of 40%. Note that histopathology can detect micrometastatic disease. Such microscopic disease is clinically relevant, as the goal of imaging is to find all sites of malignancy rather than just large deposits. However, such micrometastases may be too small for reliable detection by any imaging method. This issue likely contributed to the relatively low observed sensitivity.

Table 12. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, without region matching

Diagnostic Performance Measure (n=252)	Reader 1	Reader 2	Reader 3
True positive	26	19	25
False positive	4	2	7
False negative	36	43	37
True negative	186	188	183
Sensitivity, point estimate (95% CI)	0.42 (0.30, 0.54)	0.31 (0.19, 0.42)	0.40 (0.28, 0.53)
Specificity, point estimate (95% CI)	0.98 (0.95, 0.99)	0.99 (0.96, 1)	0.96 (0.94, 0.99)
PPV, point estimate (95% CI)	0.87 (0.70, 0.95)	0.90 (0.70, 0.99)	0.78 (0.64, 0.92)
NPV, point estimate (95% CI)	0.84 (0.79, 0.89)	0.81 (0.76, 0.86)	0.83 (0.78, 0.88)
% pathology positive, point estimate (95% CI)	0.25 (0.19, 0.30)	0.25 (0.19, 0.30)	0.25 (0.19, 0.30)

Source: PyL 2301 (OSPREY) Clinical Study Report, Table 16, FDA clinical reviewer analysis (PPV, NPV, % pathology positive).
Abbreviations: CI = confidence interval, n = number of patients, NPV = negative predictive value, PPV = positive predictive value

Of important note, in all readers the PPV was greater than the percentage of patients in the trial who had pelvic lymph node metastasis confirmed by histopathology, which is comparable to the prevalence in the intended population of use. This finding demonstrates that for the studied clinical setting, the test provides added diagnostic information in the subgroup of patients who are test positive. Accounting for the 95% confidence intervals, the NPV does not exceed the fraction of patients who have no histopathology positive pelvic lymph nodes, raising the possibility that a negative test may add little useful information in this patient population.

The Applicant's primary analysis allows any PET positive pelvic lymph node to match any histopathology positive pelvic lymph node. For many treatment approaches, correctly identifying patients with pelvic lymph node metastases is sufficient. However, identifying the location of pelvic lymph node metastases might be important for other treatment strategies. To attempt to address this issue, a region-based approach was used with the pelvic lymph nodes separated into left, right, and other regions. For patients with different categorization among the regions, the Applicant provided two different analyses, using the priority TP>FP>FN>TN or the priority TP > FN > FP >TN to convert region-level results to patient-level results.

As pointed out by the Applicant at a meeting with FDA held on May 15, 2019, in the pre-prostatectomy setting, false negative PET results are expected to be less clinically relevant than false positive results. Existing management protocols already incorporate low sensitivity conventional imaging and the potential consequences of a false positive result, namely prohibiting a patient from curative-intent treatment, can be considered less favorable than a false negative result in which planned treatment would likely proceed as if PET had not been performed. Therefore, the Applicant considers the priority TP > FP > FN > TN to be more clinically relevant. The FDA clinical review team agrees, and results using this classification scheme are shown in Table 13. Relatively few patients were categorized differently from the Applicant's primary analysis, but there was a slight trend to lower PPV. Note that false positive was given priority over false negative for subsequent analyses with region matching.

Table 13. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, without and with region matching

Diagnostic Performance Measure (n=252)	Reader 1		Reader 2		Reader 3	
	No Region Matching	Region Matched	No Region Matching	Region Matched	No Region Matching	Region Matched
True positive	26	23	19	17	25	23
False positive	4	7	2	4	7	9
False negative	36	36	43	43	37	37
True negative	186	186	188	188	183	183
Sensitivity, point estimate (95% CI)	0.42 (0.30, 0.54)	0.39 (0.27, 0.51)	0.31 (0.19, 0.42)	0.28 (0.17, 0.40)	0.40 (0.28, 0.53)	0.38 (0.26, 0.51)
Specificity, point estimate (95% CI)	0.98 (0.95, 0.99)	0.96 (0.94, 0.99)	0.99 (0.96, 1)	0.98 (0.95, 0.99)	0.96 (0.94, 0.99)	0.95 (0.92, 0.98)
PPV, point estimate (95% CI)	0.87 (0.70, 0.95)	0.77 (0.62, 0.92)	0.90 (0.70, 0.99)	0.81 (0.59, 0.93)	0.78 (0.64, 0.92)	0.72 (0.56, 0.87)
NPV, point estimate (95% CI)	0.84 (0.79, 0.89)	0.84 (0.79, 0.89)	0.81 (0.76, 0.86)	0.81 (0.76, 0.86)	0.83 (0.78, 0.88)	0.83 (0.78, 0.88)
% pathology positive, point estimate (95% CI)	0.25 (0.19, 0.30)	0.23 (0.18, 0.29)	0.25 (0.19, 0.30)	0.24 (0.19, 0.29)	0.25 (0.19, 0.30)	0.24 (0.19, 0.29)

Source: PyL 2301 (OSPREY) Clinical Study Report, Table 16, Clinical Information Amendment of 4/6/2021, Table 1.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PPV = positive predictive value

It should be noted that the performance results presented in Table 12 and Table 13 as well as in the remainder of Section 8.1.2 are based only on patients who underwent surgery and had histopathology results available for the pelvic lymph nodes (Evaluable Set). A tipping point analysis and refined imputation that included the 16 patients without histopathology were also performed, see Statistical Evaluation Section 8.3.1, Table 44 and Table 45.

The patients included in Cohort A of this study had high risk or very high risk disease by NCCN criteria. Exploratory subgroup analyses were performed to explore the impact of individual risk factors on the primary efficacy results. The baseline PSA level, either grouped as <10 ng/mL versus 10-20 ng/mL versus >20 ng/mL or as ≤ median versus > median, did not show recognizable trends in sensitivity or specificity (data not shown). As shown in Table 14, there appears to be a trend to higher numbers of true positive patients on piflufolastat F 18 PET for patients with total Gleason score of 8 or greater.

Table 14. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, stratified by total Gleason score

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	Gleason ≤7 (n=49)	Gleason ≥8 (n=203)	Gleason ≤7 (n=49)	Gleason ≥8 (n=203)	Gleason ≤7 (n=49)	Gleason ≥8 (n=203)
True positive	2	21	1	16	2	21
False positive	0	7	0	4	1	8
False negative	8	28	9	34	8	29
True negative	39	147	39	149	38	145
Sensitivity, point estimate (95% CI)	0.20 (0.05. 0.52)	0.43 (0.29, 0.57)	0.10 (0, 0.43)	0.32 (0.19, 0.45)	0.20 (0.05, 0.52)	0.42 (0.28, 0.56)

Specificity, point estimate (95% CI)	1 (0.89, 1)	0.95 (0.92, 0.99)	1 (0.89, 1)	0.97 (0.93, 0.99)	0.97 (0.86, 1)	0.95 (0.91, 0.98)
PPV, point estimate (95% CI)	1 (0.29, 1)	0.75 (0.59, 0.91)	1 (0.17, 1)	0.80 (0.58, 0.93)	0.67 (0.20, 0.94)	0.72 (0.56, 0.89)
NPV, point estimate (95% CI)	0.83 (0.72, 0.94)	0.84 (0.79, 0.89)	0.81 (0.70, 0.92)	0.81 (0.76, 0.87)	0.83 (0.72, 0.94)	0.83 (0.78, 0.89)
% pathology positive, point estimate (95% CI)	0.20 (0.09, 0.32)	0.24 (0.18, 0.30)	0.20 (0.09, 0.32)	0.25 (0.19, 0.31)	0.20 (0.09, 0.32)	0.25 (0.19, 0.31)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PPV = positive predictive value

An apparent subgroup difference was also observed for the tumor stage risk factor (Table 15). The analysis cutpoint of ≤ T2b versus ≥ T2c was chosen based on the D'Amico risk categorization scheme (D'Amico et al., 1998). However, accounting for smaller subgroups, similar results were found using NCCN cutpoints of ≤ T2a, T2b-T2c, and ≥ T3a (data not shown). There was a trend to higher sensitivity in patients with the higher risk tumor stage. There was also a trend to increased PPV with higher tumor stage.

Table 15. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, stratified by tumor stage

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	≤ T2b (n=156)	≥ T2c (n=82)	≤ T2b (n=156)	≥ T2c (n=82)	≤ T2b (n=156)	≥ T2c (n=82)
True positive	7	15	6	11	9	13
False positive	5	1	3	1	5	3
False negative	24	10	26	14	23	12
True negative	120	56	121	56	119	54
Sensitivity, point estimate (95% CI)	0.23 (0.08, 0.37)	0.60 (0.41, 0.79)	0.19 (0.05, 0.32)	0.44 (0.25, 0.63)	0.28 (0.13, 0.44)	0.52 (0.32, 0.72)
Specificity, point estimate (95% CI)	0.96 (0.93, 0.99)	0.98 (0.90, 1)	0.98 (0.93, 0.99)	0.98 (0.90, 1)	0.96 (0.93, 0.99)	0.95 (0.85, 0.99)
PPV, point estimate (95% CI)	0.58 (0.30, 0.86)	0.94 (0.7, 1)	0.67 (0.35, 0.88)	0.92 (0.62, 1)	0.64 (0.39, 0.89)	0.81 (0.56, 0.94)
NPV, point estimate (95% CI)	0.83 (0.77, 0.89)	0.85 (0.76, 0.93)	0.82 (0.76, 0.88)	0.80 (0.71, 0.89)	0.84 (0.78, 0.90)	0.82 (0.73, 0.91)
% pathology positive, point estimate (95% CI)	0.20 (0.14, 0.26)	0.30 (0.21, 0.40)	0.21 (0.14, 0.27)	0.30 (0.21, 0.40)	0.21 (0.14, 0.27)	0.30 (0.21, 0.40)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PPV = positive predictive value
Note: A total of 14 out of 252 patients in the Evaluable Set were excluded from this analysis due to insufficient tumor stage information. This includes 6 patients categorized as T2 and 8 patients categorized as TX.

Patients in the Evaluable Set were evenly distributed between those at least 65 years of age and those who were younger. There was little difference between these subgroups for sensitivity or specificity (Table 16). Analyses by race or ethnicity were not performed due to small subgroup sizes. Analysis by sex is not possible as only males were enrolled in the trial.

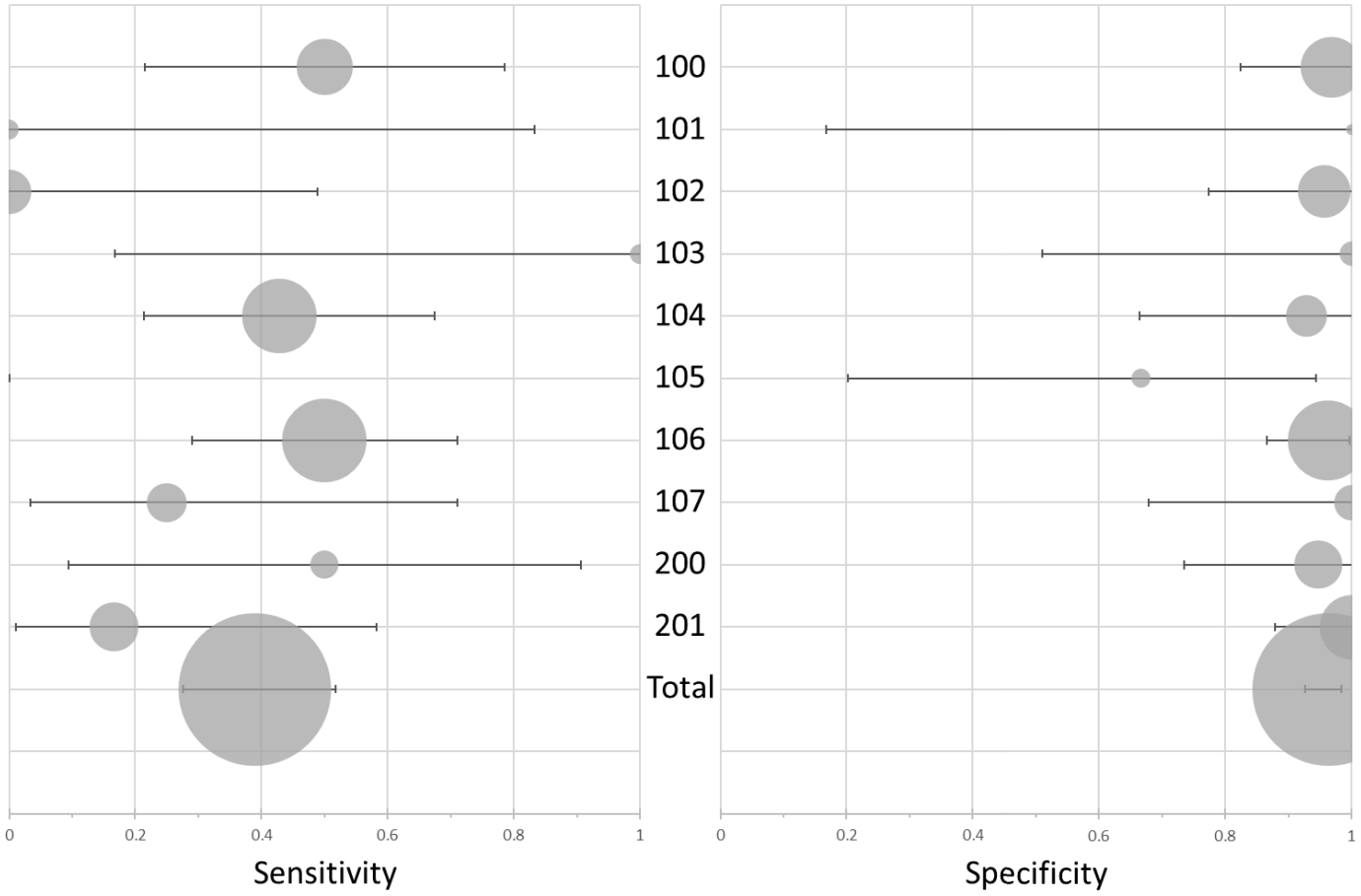
Table 16. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, stratified by age

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	Age ≤ 64 (n=126)	Age ≥ 65 (n=126)	Age ≤ 64 (n=126)	Age ≥ 65 (n=126)	Age ≤ 64 (n=126)	Age ≥ 65 (n=126)
True positive	13	10	10	7	13	10
False positive	2	5	2	2	4	5
False negative	20	16	23	20	21	16
True negative	91	95	91	97	88	95
Sensitivity, point estimate (95% CI)	0.39 (0.23, 0.56)	0.38 (0.20, 0.57)	0.30 (0.15, 0.46)	0.26 (0.09, 0.42)	0.38 (0.22, 0.55)	0.38 (0.20, 0.57)
Specificity, point estimate (95% CI)	0.98 (0.92, 1)	0.95 (0.91, 0.99)	0.98 (0.92, 1)	0.98 (0.92, 1)	0.96 (0.89, 0.99)	0.95 (0.91, 0.99)
PPV, point estimate (95% CI)	0.87 (0.61, 0.98)	0.67 (0.43, 0.91)	0.83 (0.54, 0.97)	0.78 (0.44, 0.95)	0.76 (0.52, 0.91)	0.67 (0.43, 0.91)
NPV, point estimate (95% CI)	0.82 (0.75, 0.89)	0.86 (0.79, 0.92)	0.80 (0.72, 0.87)	0.83 (0.76, 0.90)	0.81 (0.73, 0.88)	0.86 (0.79, 0.92)
% pathology positive, point estimate (95% CI)	0.26 (0.19, 0.34)	0.21 (0.14, 0.28)	0.26 (0.19, 0.34)	0.21 (0.14, 0.29)	0.27 (0.19, 0.35)	0.21 (0.14, 0.28)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PPV = positive predictive value

Primary endpoint results stratified by study site for Reader 1 are shown in Figure 5. The sites that contributed the most patients to the Evaluable Set were site 106 (n=71), site 201 (n=40), and site 100 (n=39). No extreme outliers are identified. Sites 100 through 107 were located in the United States and sites 200 and 201 were in Canada. There does not appear to be a substantial regional trend in sensitivity or specificity. Some investigators at sites 100 and 104 had disclosable financial interests. The confidence intervals for these sites' estimates of sensitivity and specificity overlap with the overall point estimate values for the study.

Figure 5. Patient-level sensitivity and specificity of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, stratified by study site, Reader 1 only



Source: FDA clinical reviewer analysis.
Abbreviations: FN = false negative, FP = false positive
Note: Relative bubble size reflects number of patients analyzable for the parameter, not total enrollment at the site. Error bars are 95% confidence intervals (Agresti-Coull). Site 105 had no true positive or false negative patients for Reader 1, so sensitivity cannot be determined.

Data Quality and Integrity

FDA Office of Scientific Investigations audits of the Applicant, the contract research organization that performed the PET reads, and selected clinical trial sites revealed no significant GCP deficiencies.

A total of four investigators at sites (b) (6) reported disclosable financial interests. As shown in Table 17, excluding the 67 patients enrolled at these sites did not substantially change the estimates of sensitivity or specificity compared to the Evaluable Set.

Table 17. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, excluding sites with investigators who reported disclosable financial interests

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	All sites (n=252)	Excluding (b) (6) (n=185)	All sites (n=252)	Excluding (b) (6) (n=185)	All sites (n=252)	Excluding (b) (6) (n=185)
True positive	23	13	17	11	23	14
False positive	7	5	4	3	9	5
False negative	36	24	43	27	37	24
True negative	186	143	188	144	183	142
Sensitivity, point estimate (95% CI)	0.39 (0.27, 0.51)	0.35 (0.20, 0.51)	0.28 (0.17, 0.40)	0.29 (0.15, 0.43)	0.38 (0.26, 0.51)	0.37 (0.22, 0.52)
Specificity, point estimate (95% CI)	0.96 (0.94, 0.99)	0.97 (0.94, 1)	0.98 (0.95, 0.99)	0.98 (0.94, 1)	0.95 (0.92, 0.98)	0.97 (0.94, 1)
PPV, point estimate (95% CI)	0.77 (0.62, 0.92)	0.72 (0.52, 0.93)	0.81 (0.59, 0.93)	0.79 (0.52, 0.93)	0.72 (0.56, 0.87)	0.74 (0.54, 0.93)
NPV, point estimate (95% CI)	0.84 (0.79, 0.89)	0.86 (0.80, 0.91)	0.81 (0.76, 0.86)	0.84 (0.79, 0.90)	0.83 (0.78, 0.88)	0.86 (0.80, 0.91)
% pathology positive, point estimate (95% CI)	0.23 (0.18, 0.29)	0.20 (0.14, 0.26)	0.24 (0.19, 0.29)	0.21 (0.15, 0.26)	0.24 (0.19, 0.29)	0.21 (0.15, 0.26)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PPV = positive predictive value

Dose/Dose Response

A single dose range of 8 mCi to 10 mCi piflufolastat F 18 was used in this study. For the Safety Set, the decay-corrected administered dose was 9.18 ± 0.63 mCi (mean ± standard deviation). Twelve of 268 patients (4%) received doses of less than 8 mCi, ranging as low as 6.55 mCi. Three of 268 patients (1%) received doses greater than 10 mCi, ranging up to 10.5 mCi.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Both inter-reader and intra-reader variability were examined for the overall PET result in the pelvic lymph nodes. Inter-reader variability was assessed using Fleiss' kappa, with kappa in the Safety Set reported [PyL 2301 (OSPREY) Clinical Study Report, Table 28] as 0.78 (95% confidence

interval: 0.71, 0.85). Intra-reader variability assessment was through re-reads of 21 scans per reader incorporated into each reader's worklist in a blinded manner. Readers 1 and 3 had 100% concordance between the initial and repeat reads at the overall pelvic lymph node level, while reader 2 was concordant for 19 of 21 scans (91%).

While the primary endpoints of this study were based on estimates of piflufolastat F 18 PET ability to detect pelvic lymph node metastases, exploratory analyses were also performed for other body regions. In the prostate gland, PET positive foci consistent with prostate cancer were reported in almost all patients in the Evaluable Set, as shown in Table 18. A prostate gland surgical histopathology standard was available for 247 patients and the lower bound of the 95% confidence interval for sensitivity was 92% for the lowest performing reader [PyL 2301 (OSPREY) Clinical Study Report, Table 25]. However, the readers could not practically be blinded to the knowledge that all patients had prostate cancer, and these results are not applicable to patients where a prostate cancer diagnosis has not been made by biopsy. Beyond the prostate, the most common site of PET positivity was the lymph nodes. No systematic collection of reference standard data was performed for extrapelvic lymph node, soft tissue, or bone lesions, so sensitivity and specificity estimates cannot be made for these regions.

Table 18. Number of patients with at least one piflufolastat F 18 positive lesion, by region

Region (n=252)	Reader 1 n PET positive (%)	Reader 2 n PET positive (%)	Reader 3 n PET positive (%)
Prostate gland	247 (98%)	247 (98%)	238 (94%)
Lymph nodes (pelvic and extrapelvic)	36 (14%)	26 (10%)	34 (13%)
Soft tissue	11 (4%)	3 (1%)	12 (5%)
Bone	18 (7%)	5 (2%)	15 (6%)

Source: PyL 2301 (OSPREY) Clinical Study Report, Table 23.
Abbreviations: n = number of patients, PET = positron emission tomography

An exploratory analysis of the number of dissected, histopathology positive, and PET positive pelvic lymph nodes is shown in Table 19. To limit the size of the table, only the results for reader 1 are shown. The average number of dissected lymph nodes is not markedly lower in the patients categorized as disease negative than those considered disease positive. In patients categorized as true positive, there is a trend to lower mean number of positive nodes by PET than by histopathology. This is compatible with the relatively low sensitivity seen in earlier analyses and likely reflects the presence of micrometastases, at least in part. Trends to higher number of pathology positive nodes for true positive patients versus false negative patients and to higher number of PET positive nodes for true positive patients than false positive patients both suggest that the performance of the PET is influenced by the extent of pelvic lymph node disease. This suggestion is further supported by the trend to higher performance in patients

with higher Gleason score (Table 14) and tumor stage (Table 15), which are associated with increased likelihood of pelvic lymph node disease.

Table 19. Pelvic lymph node counts stratified by patient-level categorization with region matching, Reader 1 only

Patient-Level Categorization	Number of Patients	Number of Nodes Dissected		Number of Nodes Positive by Pathology		Number of Nodes Positive by PET	
		Mean	Range	Mean	Range	Mean	Range
True positive	23	24	8-48	3.4	1-8	2.4	1-6
False positive	7	18	5-30	0.7	0-3	1.4	1-2
False negative	36	20	4-51	1.8	1-7	0.03	0-1
True negative	186	16	1-51	0	0	0.02	0-1

Source: FDA clinical reviewer analysis.
Abbreviations: FN = false negative, FP = false positive, PET = positron emission tomography
Note: Some patients categorized as false positive could have positive lymph nodes at pathology due to discordant location of the nodes between PET and surgery. Some patients categorized as false negative or true negative could have positive lymph nodes on PET because PET positive pelvic lymph nodes located in regions that were not dissected were not considered for the primary analysis.

As shown in Table 11, approximately 38% of patients in the study had pelvic lymphadenopathy by baseline conventional imaging and 17% had distant metastatic disease. Because these patients may have larger disease volume and thus be easier to diagnose, a subgroup analysis was performed to compare patients who had evidence of extra-prostatic disease by conventional imaging and those who did not (Table 20). Patients with negative conventional imaging trended to lower sensitivity than those who were positive on conventional imaging. However, specificity remained high in both subgroups, and for two of three readers the lower bound of the PPV estimate for the conventional imaging negative subgroup remained above the upper bound of the histopathology positive fraction estimate. Note that most baseline conventional imaging appears to have been obtained after study entry, as Table 12 of the PyL 2301 (OSPREY) Clinical Study Report indicates that only nine (3.4%) patients were considered N1 and one patient M1 at study entry. This point suggests that biased enrollment based on conventional imaging status was unlikely and that the performance estimates obtained in the primary analyses would apply to appropriately selected patients even if conventional imaging was not performed.

Table 20. Patient-level performance of piflufolastat F 18 for detection of pelvic lymph node metastases, with region matching, stratified by baseline conventional imaging results

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	N0 M0 (n=147)	Other (n=103)	N0 M0 (n=147)	Other (n=103)	N0 M0 (n=147)	Other (n=103)
True positive	6	17	6	11	7	16
False positive	5	2	2	2	5	4
False negative	21	14	22	20	21	15
True negative	115	70	117	70	114	68
Sensitivity, point estimate (95% CI)	0.22 (0.07, 0.38)	0.55 (0.37, 0.72)	0.21 (0.06, 0.37)	0.35 (0.19, 0.52)	0.25 (0.09, 0.41)	0.52 (0.34, 0.69)
Specificity, point estimate (95% CI)	0.96 (0.92, 0.99)	0.97 (0.90, 1)	0.98 (0.94, 1)	0.97 (0.90, 1)	0.96 (0.92, 0.99)	0.94 (0.86, 0.98)

PPV, point estimate (95% CI)	0.55 (0.25, 0.84)	0.89 (0.67, 0.98)	0.75 (0.40, 0.94)	0.85 (0.57, 0.97)	0.58 (0.30, 0.86)	0.80 (0.58, 0.93)
NPV, point estimate (95% CI)	0.85 (0.78, 0.91)	0.83 (0.75, 0.91)	0.84 (0.78, 0.90)	0.78 (0.69, 0.86)	0.84 (0.78, 0.91)	0.82 (0.74, 0.90)
% pathology positive, point estimate (95% CI)	0.18 (0.12, 0.25)	0.30 (0.21, 0.39)	0.19 (0.13, 0.25)	0.30 (0.21, 0.39)	0.19 (0.13, 0.25)	0.30 (0.21, 0.39)

Source: FDA clinical reviewer analysis.
Note: Two patients in the Evaluable Set had unevaluable baseline conventional imaging and were excluded from this analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, N0 M0 = no evidence of regional nodal or distant metastases, NPV = negative predictive value, PPV = positive predictive value

A further exploratory analysis comparing the ability of piflufolastat F 18 PET to detect pelvic lymph node metastases to conventional imaging is shown in Table 21. For this analysis, the conventional imaging relied on was almost exclusively CT, with only 3 patients (1.1%) having MRI. Bone scan was also performed, but is not expected to contribute to detection of pelvic lymph nodes. Sensitivity appeared similar between the PET and the CT, however, estimates of specificity were much higher for PET. As such, PPV was increased for PET as well.

Table 21. Patient-level performance of piflufolastat F 18 and baseline conventional imaging for detection of pelvic lymph node metastases, with region matching

Diagnostic Performance Measure	Piflufolastat F 18 PET (n=252)			Baseline Imaging (n=250)
	Reader 1	Reader 2	Reader 3	
True positive	23	17	23	22
False positive	7	4	9	66
False negative	36	43	37	35
True negative	186	188	183	127
Sensitivity, point estimate (95% CI)	0.39 (0.27, 0.51)	0.28 (0.17, 0.40)	0.38 (0.26, 0.51)	0.39 (0.26, 0.51)
Specificity, point estimate (95% CI)	0.96 (0.94, 0.99)	0.98 (0.95, 0.99)	0.95 (0.92, 0.98)	0.66 (0.59, 0.72)
PPV, point estimate (95% CI)	0.77 (0.62, 0.92)	0.81 (0.59, 0.93)	0.72 (0.56, 0.87)	0.25 (0.16, 0.34)
NPV, point estimate (95% CI)	0.84 (0.79, 0.89)	0.81 (0.76, 0.86)	0.83 (0.78, 0.88)	0.78 (0.72, 0.85)
% pathology positive, point estimate (95% CI)	0.23 (0.18, 0.29)	0.24 (0.19, 0.29)	0.24 (0.19, 0.29)	0.23 (0.18, 0.28)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, n = number of patients, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value

8.1.3. PyL 3301 (CONDOR)

Trial Design

PyL 3301 (CONDOR) was a prospective phase 3, single-arm, open-label study of piflufolastat F 18 for imaging of PSMA-expressing prostate adenocarcinoma. The study was performed in the United States and Canada. Results obtained from the Canadian participants should be applicable to the United States population. All patients had a history of biopsy-proven prostate

adenocarcinoma treated with definitive intent. They also were suspected of having recurrent prostate cancer based on PSA level, termed biochemical recurrence (BCR). The definitions for BCR were based on American Urological Association guidelines (Cookson et al., 2007) for patients who had a history of radical prostatectomy (PSA ≥0.2 ng/mL with confirmatory PSA level also ≥0.2 ng/mL) or on American Society for Therapeutic Radiology and Oncology guidelines (Roach et al., 2006) for patients with a history of other definite therapy including radiation (PSA ≥2 ng/mL above the post-therapy nadir). As a key inclusion criterion, all patients had negative or equivocal findings for prostate cancer by standard-of-care imaging workup for BCR within 60 days of the investigational PET scan. Such patients are expected to have harder to localize disease than the general BCR population because more advanced disease with larger and more numerous lesions might be more easily detected by standard-of-care imaging. Important criteria that excluded study participation were systemic prostate cancer therapy at enrollment and androgen deprivation therapy within 3 months of the investigational PET.

After enrollment and screening, each patient was administered 9 mCi ± 20% piflufolastat F 18 intravenously. As discussed in Section 6 of this review, this dose was chosen based on early phase experiments referenced by the Applicant. Approximately 1 to 2 hours after injection, PET/CT images were acquired from mid-thigh to skull vertex, with optional imaging of the lower extremities.

PET/CT images and reference standard images (described below) were collected by a contract research organization, (b) (4). These images were subsequently transferred to a second contract research organization, (b) (4) for centralized interpretation. The piflufolastat F 18 PET/CT images were evaluated by three independent, blinded radiologists. Training was required for the readers prior to participation in the study. Each reader recorded whether or not at least one PET positive lesion was present. If lesions were present, the location, size (two axial dimensions), SUVmax, and reader confidence level were recorded for each of up to 15 soft tissue lesions and 10 bone lesions. In addition, the total count of soft tissue lesions and bone lesions was provided. If PET positive lesions were found, the liver and descending thoracic aortic SUVmax were recorded. Lesion location was selected from a predefined list and subsequently remapped by the Applicant into 5 regions (prostate or prostate bed, pelvic lymph nodes, extrapelvic lymph nodes, viscera, and bone) and 19 subregions for analysis.

A composite reference standard was created, containing data obtained within 60 days of the piflufolastat F 18 PET scan. These data could be obtained from histopathology, correlative imaging, or PSA response to localized (radiation) therapy. The decisions of whether to obtain reference standard information and method to be used were made by site investigators based on local piflufolastat F 18 PET read results. Histopathology results could be derived from surgical material or image-guided biopsy. Correlative imaging could include images obtained during an image-guided biopsy if the histopathology result was not informative.

If follow up correlative imaging or image-guided biopsy was performed, those images were evaluated by a two member central “truth panel” and consensus results were reported. Truth

panel readers were distinct from the investigational PET readers and were blinded to piflufolastat F 18 PET reads. The truth panel readers were given the piflufolastat F 18 PET images (including annotations of PET positive lesions made by local readers) and any available baseline standard-of-care imaging.

For CT or MRI follow up correlative imaging, the truth panel categorized lesions as positive for prostate cancer using the following definitions:

- Prostate/prostate bed: Reviewers were "fairly confident" based on the imaging study alone that there was a "lesion suspicious of prostate cancer" with "imaging features consistent with tumor".
- Lymph node: To be considered abnormal, the node had to be ≥10 mm in short axis dimension *or* show interval enlargement from pre-PET imaging (threshold for enlargement not specified) *or* have "other features of an abnormal node" such as rounded morphology or loss of fatty hilum.
- Viscera: A piflufolastat F 18 positive focus had to correspond to a lesion on CT or MRI that was unequivocally present and not accounted for by a benign process.
- Bone: A piflufolastat F 18 positive focus had to correspond to a focal abnormality that was not accounted for by a benign process.

For bone scan, choline PET, or fluciclovine PET, a reference standard positive lesion was defined by abnormal uptake irrespective of the anatomic images. No criteria were provided for ultrasound images, which were exclusively presented through image-guided biopsies.

For each reference standard positive lesion identified on correlative imaging (up to 15 visceral and 10 bone lesions), the truth panel specified anatomic location, size (two axial dimensions), and whether it was defined as a lesion on each available correlative imaging modality (CT, MRI, fluciclovine PET, choline PET, or bone scan). The truth panel separately documented the total numbers of bone and non-bone lesions identified for each patient.

Images from image-guided biopsies were evaluated for whether a lesion was successfully targeted and whether the lesion was piflufolastat F 18 positive.

Inclusion of the PSA response component in the reference standard was allowed only in patients who were without evaluable histopathology or informative conventional imaging and had received only locoregional radiotherapy within 60 days following piflufolastat F 18 PET. They were followed for up to 9 months, and a PSA response indicating a reference standard positive lesion was defined as a ≥50% decline in PSA from baseline, verified by a repeat PSA draw within 4 weeks.

Lesions were matched at the region-level for histopathology reference data, at the subregion-level for imaging reference data, and at the patient-level if PSA response was used. Lesions that were both piflufolastat F 18 PET positive and reference standard positive were considered true positive, and lesions that were piflufolastat F 18 PET positive and reference standard negative

were considered false positive. If a patient had both true positive and false positive lesions, they were assigned the true positive status for patient-level analyses. PET negative patients were not considered in the primary analysis because reference standard data was not systematically collected.

Study procedures are summarized in Table 22.

Table 22. PyL 3301 (CONDOR) schedule of events

	Screening	Piflufolastat F 18 Dosing & Imaging		Safety Phone call	Efficacy follow-up	
Day	**-30 to 1**	**1**	**1 (60-120 min post-dosing)**	**8 (±3)**	**2 to 60**	**Every 3 months following initiation of locoregional RT, up to 9 months**
Informed Consent & Eligibility	X					
Demographics	X					
Medical History	X					
Prior Medications and Prior Cancer Treatments	X					
Vital Signs (blood pressure, heart rate)		X (pre-dosing)	X			
PSA (Total)	X					X
Conventional imaging	X				X	
Piflufolastat F 18 Administration		X				
Whole body PyL PET/CT			X			
Surgery or image-guided biopsy & histopathology					X	
Locoregional radiation therapy per investigator discretion					X	
Treatment-emergent Adverse Events		X		X		
Concomitant Medications and Procedures		X		X	X	X
Medical Management Questionnaire	X				X	

Source: Table 3 of PyL 3301 (CONDOR) Protocol.

Study Endpoints

The PyL 3301 (CONDOR) protocol defined the primary endpoint of correct localization rate (CLR) as "the percentage of subjects for whom there is a one-to-one correspondence between localization of at least one lesion identified on ^{18}F-DCFPyL PET/CT imaging and the composite truth standard". As noted in a Type C meeting written response letter dated September 20,

2018, there was some ambiguity in this endpoint because the population it would be applied to is undefined. This issue was discussed at a Type C meeting on October 22, 2018, and the Applicant clarified that CLR would be assessed in patients with positive piflufolastat F 18 PET scans and evaluable reference standard information. Thus, the Applicant's understanding of CLR functionally represents a patient-level positive predictive value (PPV) metric. Because of the ambiguity of the CLR definition, this primary endpoint will be referred to as PPV throughout Section 8.1.4.

Because of the high disease prevalence in patients with biochemically recurrent prostate cancer, and because it is difficult to identify true negative regions in this setting without long-term follow up, specificity is often not considered a practical endpoint for PET drug trials in the BCR population. However, PPV can also provide some information related to false positive patients and is much more readily estimated. While not included in the protocol, the patient-level correct detection rate (CDR), defined as the proportion of true positive patients among all patients scanned with piflufolastat F 18 PET and evaluated by the central readers, is described as exploratory in the statistical analysis plan. In the BCR population, this metric can provide information about false negative patients and supplement PPV results.

Another important exploratory endpoint is "detection rate", defined as the rate of piflufolastat F 18 PET positivity irrespective of reference standard validation. This metric is often reported for prostate cancer imaging methods as a function of baseline PSA level. Higher detection rates are typically observed with increasing PSA level since this marker is correlated with overall disease burden.

Statistical Analysis Plan

Applicant-defined populations of interest include:

- Safety Set: all patients who received any amount of piflufolastat F 18
- Full Analysis Set: patients who received piflufolastat F 18 and had PET/CT imaging results from at least one central reader
- Per Protocol Set: patients in the Full Analysis Set without any major protocol deviations

Primary endpoint analysis was based on the subset of piflufolastat F 18 PET positive patients in the Full Analysis Set who also had composite reference standard results available in a PET positive region. The threshold for patient-level PPV (termed CLR by the Applicant as discussed above) was set at 0.20, against which the lower bound of the 95% confidence interval for each reader was compared. At least two of three readers would need to exceed the threshold for study success. Note that there are concerns regarding the clinical relevance of a 20% threshold for patient-level PPV, however, as will be detailed later, the results far exceeded this threshold. From an FDA perspective, a 20% threshold is considered more appropriate for a CDR endpoint, defined as the fraction of true positive patients among all patients scanned with piflufolastat F 18 PET and evaluated by the central readers.

Protocol Amendments

No protocol amendments were reported by the Applicant.

8.1.4. Study Results - PyL 3301 (CONDOR)

[Do not insert text here]

Compliance with Good Clinical Practices

The Applicant indicated that the study was performed in compliance with good clinical practice (GCP) and with oversight from site IRBs.

Financial Disclosure

The Applicant stated that two investigators (b) (6) had disclosable financial interests. The potential for bias related to these interests was minimized by the Applicant's use of an independent contract research organization to generate blinded PET reads.

Patient Disposition

A total of 208 patients were enrolled in PyL 3301 (CONDOR) and received piflufolastat F 18, comprising the Safety Set. All 208 patients completed PET/CT imaging and were evaluated by the central readers, so the Full Analysis Set and Safety Set are interchangeable. The Per Protocol Set contained 201 patients, and the 7 patients with major protocol deviations are discussed below.

The Applicant reports 13 patients (6.3%) discontinued the study. The reasons for study discontinuation are listed as significant protocol deviation or noncompliance (n=6), withdrawal by patient (n=5), sponsor decision (n=1), and investigator decision (n=1).

Protocol Violations/Deviations

Seven major protocol deviations were reported in 7 of 208 patients in the Full Analysis Set (3.4%). All major protocol deviations involved the use of androgen deprivation therapy; six patients were started on ADT after the piflufolastat F 18 PET but before obtaining reference standard data and one patient received ADT within 3 months prior to the PET. These protocol deviations are not expected to have a substantial impact on the primary analysis.

Table of Demographic Characteristics

Table 23 shows the demographic features of the patients enrolled in PyL 3301 (CONDOR). These patients were slightly older than those in the PyL 2301 trial, which is expected because the PyL 2301 trial studied patients at initial diagnosis rather than after recurrence was detected. Otherwise, the demographic features of the studies are similar and reference is made to Section 8.1.2 for additional related discussion.

Table 23. Demographics for the Safety Set of PyL 3301 (CONDOR)

Parameter	Safety Set (n=208) n (%)
Age	
Mean years (SD)	67.9 (7.8)
Median (years)	68.0
Min, max (years)	43, 91
Age Group	
< 65 years	67 (32%)
≥ 65 years	141 (68%)
Race	
White	188 (90%)
Black or African American	15 (7%)
Asian	3 (1%)
Other or not reported	2 (1%)
Ethnicity	
Hispanic or Latino	5 (2%)
Not Hispanic or Latino	196 (94%)
Not reported	7 (3%)
Region	
United States	183 (88%)
Canada	25 (12%)

Source: PyL 3301 (CONDOR) Clinical Study Report, Table 5 and FDA clinical reviewer (Region).
Abbreviations: max = maximum, min = minimum, n = number of patients, SD = standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics for the patients in this trial are listed in Table 24. For many imaging tests, including for the related PSMA PET drug Ga 68 PSMA-11, a higher PSA level is associated with an increased likelihood of a positive result. Thus, the relatively low median PSA of 0.82 ng/mL in this study is reassuring that the enrolled patients do not represent an unusually easy to diagnose group.

Most patients in the trial had been treated with radical prostatectomy and roughly half had received radiation therapy at some point prior to enrollment. A substantial minority had received androgen deprivation therapy, though as noted above this therapy was not allowed within 3 months prior to the piflufolastat F 18 PET scan. It is not stated whether any patients were considered castrate resistant.

All patients were to have been evaluated using standard of care conventional imaging for biochemical recurrence prior to enrollment, with negative or indeterminate results. Nearly two-thirds of the patients were imaged using both anatomic imaging (CT or MRI) and bone scan. An additional 20% of patients were imaged with anatomic techniques only, which is reasonable given the low sensitivity of bone scan when the PSA level is low. Anatomic imaging included the pelvis and abdomen in most patients and the chest in nearly one-half of patients. It is likely that

the exclusion of patients with positive conventional imaging at baseline resulted in a more difficult to diagnose population for this trial, which is a strength of the study design.

Table 24. Selected baseline characteristics for the Safety Set of PyL 3301 (CONDOR)

Parameter	Safety Set (n=208) n (%)
PSA	
Mean, ng/mL (SD)	3.044 (8.372)
Median, ng/mL	0.820
Min, max, ng/mL	0.17, 98.45
Prior therapies	
Radical prostatectomy	177 (85%)
Radiation therapy	105 (51%)
Androgen deprivation therapy	55 (26%)
Baseline conventional imaging	
CT or MRI only	42 (20%)
Bone scan only	15 (7%)
CT/MRI and bone scan	130 (63%)
PET (^{18}F-FDG, ^{18}F-fluciclovine, or ^{11}C-choline) with or without other modalities	21 (10%)

Source: PyL 3301 (CONDOR) Clinical Study Report, Tables 6, 7, and 8.
Abbreviations: max = maximum, min = minimum, n = number of patients, PET = positron emission tomography, SD = standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites; therefore, drug compliance is not applicable.

While all enrolled patients were included in the Full Analysis Set, only 99 to 104 patients (48% to 50%), depending on the PET reader, contributed to the primary patient-level PPV endpoint analysis below. Most of the patients excluded from the calculation had negative results on the PET scan. However, there were also 24 to 33 patients who had positive PET scans but lacked reference standard results for a PET positive lesion, representing 19% to 24% of the PET positive group. The potential impact of these patients without appropriate reference standard information were examined by exploratory analyses below and in Section 8.3.2, Statistical Evaluation.

Efficacy Results – Primary and Major Secondary Endpoints

The patient-level positive predictive value (PPV) primary endpoint result is shown in Table 25. The lower bound of the 95% confidence interval for PPV far exceeded the predefined threshold of 20% for all three readers, ranging from 78% to 80%. As mentioned above, roughly one-half of the enrolled patients were not included in this primary analysis, either because they had negative PET results or because no reference standard data were available to correspond to a PET positive region. The correct detection rate (CDR) or true positive detection rate, which includes all enrolled patients, ranged from 34% to 36% at the lower bound of the 95% confidence interval. While no predefined threshold was set by the Applicant for this parameter,

the observed values are clinically relevant in this population, as all patients had negative or equivocal conventional imaging results prior to enrollment in the trial, so any new true positive patients suggest a benefit from the study drug.

Table 25. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer

Diagnostic Performance Measure (n=208)	Reader 1	Reader 2	Reader 3
True positive	89	87	84
False positive	15	13	15
PET positive without reference standard	33	24	24
PET negative	71	84	85
Fraction PET positive*	0.66	0.60	0.59
CDR, point estimate (95% CI)	0.43 (0.36, 0.50)	0.42 (0.35, 0.49)	0.40 (0.34, 0.47)
PPV, point estimate (95% CI)	0.86 (0.79, 0.92)	0.87 (0.80, 0.94)	0.85 (0.78, 0.92)

Source: PyL 3301 (CONDOR) Clinical Study Report, Section 11.4.1.1 and Table 9, *FDA clinical reviewer analysis
Abbreviations: CDR = correct detection rate, CI = confidence interval, n = number of patients, PET = positron emission tomography, PPV = positive predictive value

It should be noted that PPV results presented in Table 25 as well as in the remainder of Section 8.1.4 are based only on PET positive patients with composite reference standard results available in a PET positive region. CDR results presented in Table 25 as well as in the remainder of Section 8.1.4 are based on all scanned patients, such that PET positive patients without composite reference standard results available in a PET positive region were included in the denominator. Multiple imputation approaches for PET positive patients without composite reference standard results in a PET positive region are detailed in the Statistical Evaluation Section 8.3.2.

The contribution of the various components of the composite reference standard to the primary results is described in Table 26. The majority of reference standard data were obtained through conventional imaging, which was used to determine the status of 70% to 73% of the patients who were evaluable for PPV. There was a slight trend to higher PPV in patients evaluated by imaging than those evaluated by histopathology, particularly for Reader 1. Among imaging modalities, ^{18}F-fluciclovine was used most often, making up 50% to 54% of the usable reference data and 71% to 74% of the imaging data.

Table 26. Component distribution for the composite reference standard in PyL 3301 (CONDOR) in patients who were evaluable for the patient-level PPV endpoint

Reference Standard Component	Reader 1 (n=104)		Reader 2 (n=100)		Reader 3 (n=99)	
	Evaluable n (%)	PPV (95% CI)	Evaluable n (%)	PPV (95% CI)	Evaluable n (%)	PPV (95% CI)
Pathology	28 (27%)	0.79 (0.63, 0.94)	29 (29%)	0.83 (0.69. 0.97)	26 (26%)	0.81 (0.66, 0.96)
Biopsy	26 (25%)	0.77 (0.61, 0.93)	26 (26%)	0.81 (0.66, 0.96)	24 (24%)	0.79 (0.63, 0.95)
Surgery	2 (2%)	1	3 (3%)	1	2 (2%)	1

		(0.29, 1)		(0.38, 1)		(0.29, 1)
Imaging	75 (72%)	0.88 (0.81, 0.95)	70 (70%)	0.89 (0.81, 0.96)	72 (73%)	0.86 (0.78, 0.94)
Fluciclovine	55 (53%)	0.91 (0.83, 0.99)	50 (50%)	0.90 (0.82, 0.98)	53 (54%)	0.87 (0.78, 0.96)
MRI	15 (14%)	0.80 (0.54, 0.94)	15 (15%)	0.87 (0.61, 0.98)	15 (15%)	0.87 (0.61, 0.98)
CT	5 (5%)	0.80 (0.36, 0.98)	4 (4%)	1 (0.45, 1)	5 (5%)	0.80 (0.36, 0.98)
Ultrasound	1 (1%)	1 (0.17, 1)	1 (1%)	1 (0.17, 1)	0	-
Bone scan	1 (1%)	0 (0, 0.83)	1 (1%)	0 (0, 0.83)	1 (1%)	0 (0, 0.83)
PSA	1 (1%)	1 (0.17, 1)	1 (1%)	1 (0.17, 1)	1 (1%)	1 (0.17, 1)

Source: PyL 3301 (CONDOR) Clinical Study Report, Table 14.2.1.12.
Abbreviations: CDR = correct detection rate, CI = confidence interval, CT = computed tomography, MRI = magnetic resonance imaging, n = number of patients, PPV = positive predictive value, PSA = prostate-specific antigen

Because of the large contribution of ^{18}F-fluciclovine PET to the composite reference standard, a subgroup analysis was performed between patients categorized by that method and those categorized by any other reference method, including histopathology (Table 27). Patients evaluated using ^{18}F-fluciclovine PET had a trend to slightly higher PPV than with other modalities, particularly for Reader 1, and this likely drives the trend to higher PPV seen with imaging reference standards in the prior table. However, even when patients characterized using ^{18}F-fluciclovine are excluded, the PPV remains high, with lower bound of the 95% confidence interval ranging from 68% to 74%.

Table 27. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer, stratified by use of ^{18}F-fluciclovine (FACBC) as a reference

Diagnostic Performance	Reader 1 (n=104)		Reader 2 (n=100)		Reader 3 (n=99)	
Measure	**FACBC**	**Other**	**FACBC**	**Other**	**FACBC**	**Other**
True positive	50	39	45	42	46	38
False positive	5	10	5	8	7	8
PPV, point estimate	0.91	0.80	0.90	0.84	0.87	0.83
(95% CI)	(0.83, 0.99)	(0.68, 0.91)	(0.82, 0.88)	(0.74, 0.94)	(0.78, 0.96)	(0.72, 0.94)

Source: FDA clinical reviewer analysis, based on data in PyL 3301 (CONDOR) Clinical Study Report, Table 14.2.1.12.
Abbreviations: CI = confidence interval, FACBC = ^{18}F-fluciclovine , n = number of patients, PPV = positive predictive value

As shown in Table 28, the patient-level PPV was similar in patients younger than 65 years old and those 65 or older. There was, however, a trend to higher CDR in the older patients. For a related radiopharmaceutical, Ga 68 PSMA-11, there are conflicting literature reports regarding whether older age is associated with higher PET positivity rate in patients with BCR (Afshar-Oromieh et al., 2021; Chevalme et al., 2021), and the significance of this trend is unclear. Analyses by race or ethnicity were not performed due to small subgroup sizes. Analysis by sex is not possible as only males were enrolled in the trial.

Table 28. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer, stratified by age

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	Age ≤ 64 (n=67)	Age ≥ 65 (n=141)	Age ≤ 64 (n=67)	Age ≥ 65 (n=141)	Age ≤ 64 (n=67)	Age ≥ 65 (n=141)
True positive	21	68	21	66	19	65
False positive	4	11	4	9	5	10
PET positive without reference standard	13	20	9	15	10	14
PET negative	29	42	33	51	33	52
Fraction PET positive	0.57	0.70	0.51	0.64	0.51	0.63
CDR, point estimate	0.31	0.48	0.31	0.47	0.28	0.46
(95% CI)	(0.20, 0.42)	(0.40, 0.56)	(0.20, 0.42)	(0.39, 0.55)	(0.18, 0.39)	(0.38, 0.54)
PPV, point estimate	0.84	0.85	0.84	0.88	0.79	0.87
(95% CI)	(0.65, 0.94)	(0.78, 0.94)	(0.65, 0.94)	(0.81, 0.95)	(0.63, 0.95)	(0.79, 0.94)

Source: PyL 3301 (CONDOR) Clinical Study Report, Table 14.2.1.6.
Abbreviations: CDR = correct detection rate, CI = confidence interval, n = number of patients, PET = positron emission tomography, PPV = positive predictive value

An Applicant-performed subgroup analysis (Table 29) investigated the effect of time between injection of the radiopharmaceutical and PET scan on test performance. The median time was 79 minutes and the range was 59 to 115 minutes. There were trends to higher PPV and CDR in patients with dose to scan times of 60 to 89 minutes compared to those scanned at 90 to 120 minutes. Accordingly, the prescribing information states that the "recommended start time for image acquisition is 60 minutes after PYLARIFY injection," and "starting image acquisition more than 90 minutes after injection may adversely impact imaging performance."

Table 29. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer, stratified by time between dosing and PET scan

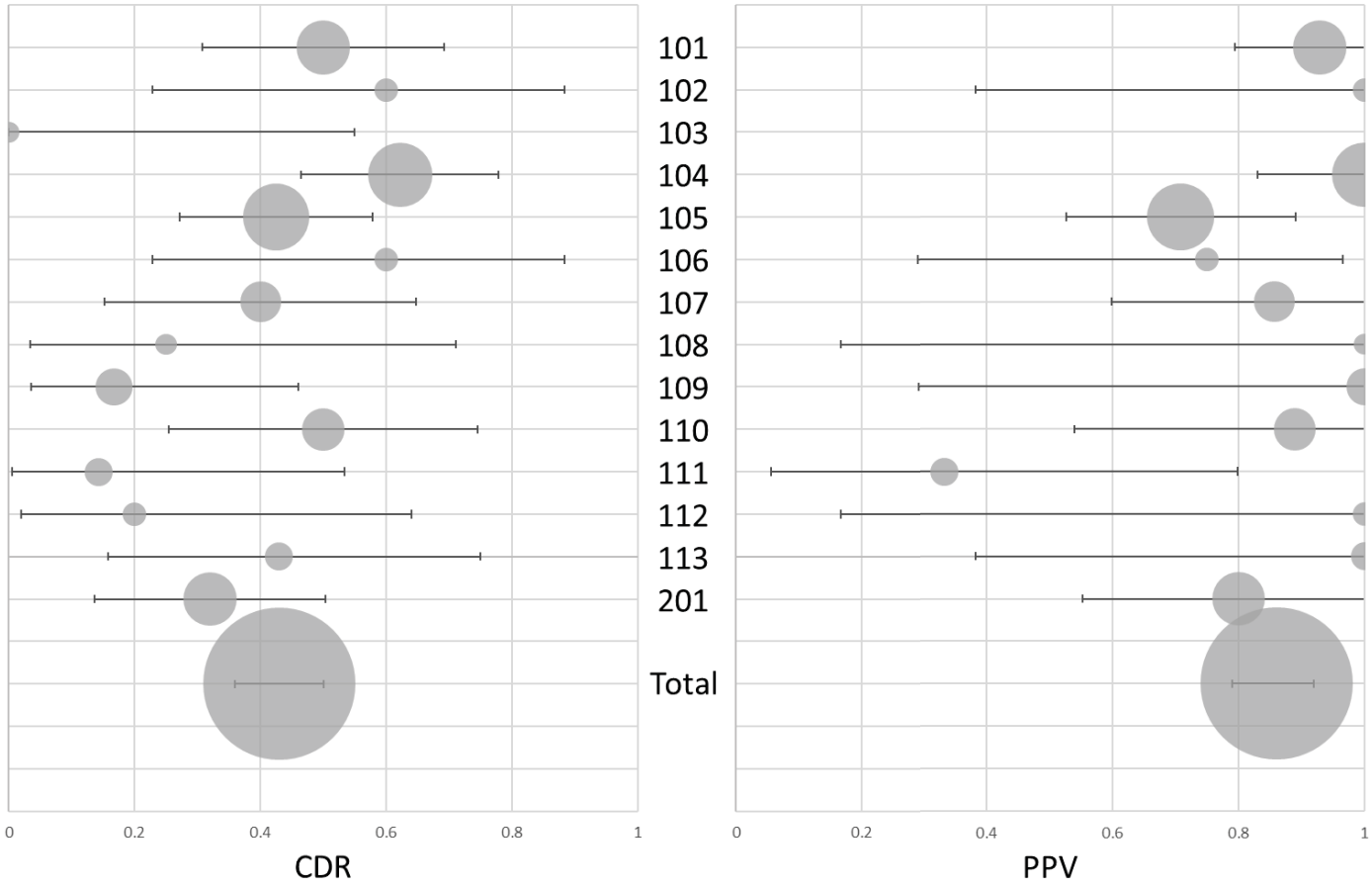
Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	DTST 60-89 min (n=155)	DTST 90-120 min (n=51)	DTST 60-89 min (n=155)	DTST 90-120 min (n=51)	DTST 60-89 min (n=155)	DTST 90-120 min (n=51)
True positive	69	18	71	14	65	17
False positive	8	7	6	7	9	6
PET positive without reference standard	23	10	18	6	18	6
PET negative	55	16	60	24	63	22
Fraction PET positive	0.65	0.69	0.61	0.53	0.59	0.57
CDR, point estimate	0.45	0.35	0.46	0.27	0.42	0.33
(95% CI)	(0.37, 0.52)	(0.22, 0.48)	(0.38, 0.54)	(0.15, 0.40)	(0.34, 0.50)	(0.20, 0.46)
PPV, point estimate	0.90	0.72	0.92	0.67	0.88	0.74
(95% CI)	(0.83, 0.96)	(0.54, 0.90)	(0.86, 0.98)	(0.47, 0.87)	(0.80, 0.95)	(0.56, 0.92)

Source: PyL 3301 (CONDOR) Clinical Study Report, Table 17.
Abbreviations: CDR = correct detection rate, CI = confidence interval, DTST = dose to scan time, n = number of patients, PET = positron emission tomography, PPV = positive predictive value
Note: Two patients were scanned at less than 60 minutes after dosing and are excluded from this table.

Results for the patient-level PPV and CDR endpoints stratified by study site are shown in Figure 6 for Reader 1. The sites with the largest enrollment were 105 (n=40), 104 (n=37), and 101 (n=26). These sites also contributed the most patients who were evaluable for the primary

patient-level PPV endpoint, with 24, 23, and 14 patients, respectively. Sites 101 through 113 were located in the United States and site 201 in Canada. The Canadian site was the fourth largest, enrolling 25 patients, 10 of whom contributed to the PPV evaluation. The confidence intervals from the Canadian site overlap the PPV and CDR point estimates for the overall results. No extreme outliers are identified.

Figure 6. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer, stratified by study site, Reader 1 only



Source: FDA clinical reviewer, based on data in PyL 3301 (CONDOR) Clinical Study Report, Table 14.2.1.11
Abbreviations: CDR = correct detection rate, PPV = positive predictive value
Note: Relative bubble size reflects total enrollment at the site. Error bars are 95% confidence intervals. Site 103 had no true positive or false positive patients for Reader 1, so PPV cannot be determined.

Data Quality and Integrity

FDA OSI audits of the Applicant, the contract research organization that performed the PET reads, and selected clinical trial sites revealed no significant GCP deficiencies.

Two investigators at site (b) (6) reported disclosable financial interests. As shown in Table 30, when results from this site are excluded, there is only minimal change in PPV or CDR compared to the full data set.

Table 30. Patient-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer, excluding sites with investigators who reported disclosable financial interests

Diagnostic Performance Measure	Reader 1		Reader 2		Reader 3	
	All sites (n=208)	Excluding (b) (6) (n=171)	All sites (n=208)	Excluding (b) (6) (n=171)	All sites (n=208)	Excluding (b) (6) (n=171)
True positive	89	66	87	64	84	65
False positive	15	15	13	13	15	15
PET positive without reference standard	33	28	24	20	24	20
PET negative	71	62	84	74	85	71
Fraction PET positive	0.66	0.64	0.60	0.57	0.59	0.58
CDR, point estimate	0.43	0.39	0.42	0.37	0.40	0.38
(95% CI)	(0.36, 0.50)	(0.31, 0.46)	(0.35, 0.49)	(0.30, 0.45)	(0.34, 0.47)	(0.31, 0.45)
PPV, point estimate	0.86	0.81	0.87	0.83	0.85	0.81
(95% CI)	(0.79, 0.92)	(0.73, 0.90)	(0.80, 0.94)	(0.75, 0.91)	(0.78, 0.92)	(0.73, 0.90)

Source: FDA clinical reviewer, based on data in PyL 3301 (CONDOR) Clinical Study Report, Table 14.2.1.11
Abbreviations: CDR = correct detection rate, CI = confidence interval, n = number of patients, PET = positron emission tomography, PPV = positive predictive value

Dose/Dose Response

The dose range for this study was 7.2 to 10.8 mCi of piflufolastat F 18. The administered dose was 9.38 mCi ± 0.68 mCi (mean ± standard deviation). One patient received a dose outside the prescribed range, 11.07 mCi. Note that the dose range for this trial was wider than that used in PyL 2301 (OSPREY), which was 8 to 10 mCi. A total of 31 of 208 (15%) patients in PyL 3301 (CONDOR) received doses greater than 10 mCi and 8 (4%) patients received doses less than 8 mCi.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

In patients with BCR prostate cancer, the value of imaging is often more in localizing disease rather than in determining whether or not a patient has disease recurrence. Thus, exploratory analyses of region-level PPV were conducted (Table 31). The most common regions of PET positivity were the pelvic lymph nodes and prostate bed. There was a trend to lower frequency

of obtaining reference standard information for the soft tissue region. In addition, the PPV for the soft tissue region tended to be lower than other regions. However, due to the relatively low frequency of PET positivity for this region, these trends are not expected to have a major impact on the patient-level PPV result.

Table 31. Region-level performance of piflufolastat F 18 for localization of biochemically recurrent prostate cancer

Region	Reader 1		Reader 2		Reader 3	
	PET + Regions Evaluated/ Total	PPV Point estimate (95% CI)	PET + Regions Evaluated/ Total	PPV Point estimate (95% CI)	PET + Regions Evaluated/ Total	PPV Point estimate (95% CI)
Prostate/prostate bed	39/44	0.79 (0.67, 0.92)	36/42	0.83 (0.71, 0.96)	36/37	0.75 (0.61, 0.89)
Pelvic lymph node	61/78	0.67 (0.55, 0.79)	55/70	0.73 (0.61, 0.84)	55/73	0.71 (0.59, 0.83)
Other lymph node	26/33	0.62 (0.43, 0.80)	23/27	0.65 (0.46, 0.85)	23/26	0.61 (0.41, 0.81)
Soft tissue	7/12	0.29 (0.08, 0.65)	9/12	0.22 (0.05, 0.56)	6/11	0.33 (0.09, 0.70)
Bone	24/28	0.63 (0.43, 0.82)	22/24	0.64 (0.44, 0.84)	23/26	0.61 (0.41, 0.81)
Total	157/195	0.67 (0.59, 0.74)	145/175	0.70 (0.63, 0.77)	143/173	0.67 (0.60, 0.75)

Source: PyL 3301 (CONDOR) Clinical Study Report, Table 18, Clinical Information Amendment of 3/26/2021, Table 2 (Total).
Abbreviations: + = positive, CI = confidence interval, n = number of regions, PET = positron emission tomography, PPV = positive predictive value
Note: Confidence intervals in the Total row are adjusted for within-patient correlations by treating the patients as clusters. There was less than 0.5% change in each confidence interval bound compared to FDA clinical reviewer analysis, which did not adjust for within-patient correlations.

It is noted that the region-level PPV estimates are lower than the patient-level PPV estimates (Table 25), 59% to 62% for the lower bound of the 95% confidence interval versus 78% to 80%. This finding appears to be due to categorization of patients with discordant regional findings (true positive region(s) and false positive region(s) within the same patient) as true positive. Such discordant regional findings were observed in a relatively high percentage of patients (0.24, 0.25, and 0.24). Region-level PPV results by reader and by baseline PSA level are further explored in the Statistical Evaluation Section 8.3.2. Since region-level PPV may be relevant for certain uses of the radiopharmaceutical, these results were summarized in labeling.

Exploratory analyses of baseline characteristics were also performed to compare patients who had positive PET scans with and without reference standard data for at least one lesion. The baseline PSA level showed potentially interesting results, but was confounded by differences in the rate of prostatectomy between the groups. Patients with prostatectomy can be considered to have biochemical recurrence at lower PSA level than those treated non-surgically. Because most patients had a prostatectomy in this trial, Table 32 shows the baseline PSA distribution only in this subgroup. Among patients with a prostatectomy and positive PET scan, those who had reference standard data tended to have a higher PSA level than those without. Because PSA level is correlated with disease volume to some degree in this population, the patients with

reference standard information may represent those with more advanced, easier to diagnose disease. Thus, test performance may be overestimated in PyL 3301 (CONDOR). However, this concern is tempered by the relatively high observed PPV, the moderate number of patients who lacked reference standard information, and the selection of patients who had negative or equivocal conventional imaging for the trial.

Table 32. PSA level and distribution in patients who had a positive piflufolastat F 18 PET scan and history of prostatectomy, stratified by availability of reference standard data in a PET positive region

Parameter	Reader 1		Reader 2		Reader 3	
	Reference Available (n=77)	Reference Unavailable (n=27)	Reference Available (n=71)	Reference Unavailable (n=20)	Reference Available (n=71)	Reference Unavailable (n=18)
Median PSA (ng/mL)	1.26	0.48	1.30	0.50	1.26	0.48
PSA <0.5 ng/mL n (%)	15 (19%)	14 (52%)	13 (18%)	10 (50%)	15 (21%)	10 (55%)
PSA 0.5 - 2 ng/mL n (%)	35 (45%)	9 (33%)	30 (42%)	8 (40%)	32 (45%)	5 (28%)
PSA ≥2 ng/mL n (%)	27 (36%)	4 (15%)	28 (40%)	2 (10%)	24 (34%)	3 (17%)

Source: FDA clinical reviewer analysis.
Abbreviations: n = number of patients, PSA = prostate-specific antigen

It is often the case that prostate cancer recurrence is detected by rising PSA level before it can be observed on imaging studies. As with other imaging methods, piflufolastat F 18 PET is more likely to be positive at higher PSA level (Table 33), however the positivity rate is reasonable even at low levels. Note that PET positivity rate is not validated against a reference standard, but this metric allows use of the entire Full Analysis Set. It is also commonly reported in the scientific literature where it is often referred to as detection rate and used for purposes of relative test performance. There may also be a trend to better PPV with higher PSA level, but the smaller sample sizes make this more difficult to assess.

Table 33. Patient-level piflufolastat F 18 PET positivity rate, stratified by PSA level

PSA Range (ng/mL)	Patients n	PET Positive Patients n	PET Positivity Rate (95% CI)	PET Positive Patients With Composite Reference Data n	PPV (95% CI)
[0-0.5)	69	24	0.35 (0.24, 0.46)	15	0.73 (0.48, 0.90)
[0.5-1)	36	18	0.50 (0.34, 0.66)	15	0.80 (0.54, 0.94)
[1-2)	31	21	0.68 (0.51, 0.84)	18	0.83 (0.60, 0.95)
[2-∞]	63	57	0.90 (0.83, 0.98)	53	0.94 (0.84, 0.99)
Total	199	120	0.60 (0.54, 0.67)	101	0.87 (0.81, 0.94)

Source: FDA clinical reviewer analysis.
Abbreviations: CI = confidence interval, n = number of patients, PET = positron emission tomography, PPV = positive predictive value, PSA = prostate-specific antigen
Notes: Due to the size of the table, reported data are based on the majority PET result for the three readers. Three patients were excluded due to lack of majority result among the categories true positive, false positive, PET positive without reference standard, and PET negative. This table excludes six patients who did not have baseline PSA level recorded.

Reference standard information was available for 20 to 26 (varying per reader) PET negative patients, representing 28 to 30% of PET negative patients and 10% to 13% of the Full Analysis Set. This reference standard information was largely from conventional imaging, with one to three patients having histopathology results and no patient having serial PSA levels in the setting of directed therapy. Based on these data, the patient-level true negative rate in the Full Analysis Set was 2% to 3% and the patient-level false negative rate was 7% to 11%. Because reference standard data were not systematically collected for PET negative patients, the reliability of these estimates is uncertain. However, a low patient-level true negative rate would be expected in patients who have biochemically recurrent prostate cancer by standard PSA thresholds.

Both inter-reader and intra-reader variability were examined for patient-level PET positivity. Inter-reader variability was assessed for the central readers using Fleiss' kappa, with kappa in the Safety Set reported as 0.65 (95% confidence interval: 0.58, 0.73). Pairwise central reader versus local reader Cohen's kappa ranged from 0.62 (0.50, 0.73) to 0.65 (0.54, 0.75). Intra-reader variability assessment was through re-reads of 42 scans per reader incorporated into each reader's worklist in a blinded manner. The concordance between the initial and repeat read patient-level PET positivity was 98%, 100%, and 90% for Readers 1, 2, and 3, respectively.

8.1.5. PyL 2301 (OSPREY) Cohort B

Patients enrolled in Cohort B of PyL 2301 (OSPREY) were required to have conventional imaging evidence of either recurrent prostate cancer or new or progressive metastatic disease. At least one lesion needed to be amenable to percutaneous biopsy. If the patient had been treated using radiotherapy or other locally ablative therapy, the targeted lesion was required to be beyond the treatment site. Images from the piflufolastat F 18 PET scan and biopsy procedure were evaluated by three central readers who determined whether the lesion that was biopsied was PET positive. Histopathology results from the biopsies served as the reference standard. Because the patient enrollment criteria define a population outside the expected clinical use for piflufolastat F 18, data obtained from this cohort were not considered to provide primary evidence of effectiveness.

Of the 117 patients enrolled in Cohort B, 93 (79%) were included in the Evaluable Set, which required a piflufolastat F 18 PET with central read result, a conventional image-guided biopsy with images that confirmed the location of the biopsy, and a histopathology result. Two patients were excluded from the Evaluable Set because of neoplasm other than prostate adenocarcinoma on the biopsy result. The majority of PET positive lesions evaluated in this trial were located outside the pelvis (76% to 78%), and no lesions were evaluated in the prostate gland or prostate bed.

While the Applicant performed their analysis at patient-level, they stated at the meeting of February 24, 2020, that only a single lesion was biopsied per patient. Thus, it is possible to perform a lesion-level analysis as well. In this context, true negative is defined as a biopsied

lesion that was negative at PET and histopathology. Patients with true negative lesions may have had PET positive or histopathology positive lesions at other sites.

As shown in Table 34, lesion-level sensitivity ranged from 87% to 92% at the lower bound of the 95% confidence interval. The lesion-level specificity was lower and more variable between the readers, ranging from 12% to 41% at the lower bound of the 95% confidence interval. Through assessment of lesions in a variety of body regions against a histopathology reference standard, these data provide supportive evidence of effectiveness.

Table 34. Lesion-level performance of piflufolastat F 18 PET in PyL 2301 (OSPREY) Cohort B Evaluable Set

Diagnostic Performance Measure (n=93)	Reader 1	Reader 2	Reader 3
True positive	69	68	65
False positive	16	15	9
False negative	1	3	5
True negative	7	7	14
Sensitivity, point estimate (95% CI)	0.99 (0.92, 1)	0.96 (0.88, 0.99)	0.93 (0.87, 0.99)
Specificity, point estimate (95% CI)	0.30 (0.12, 0.49)	0.32 (0.12, 0.51)	0.61 (0.41, 0.81)
PPV, point estimate (95% CI)	0.81 (0.73, 0.89)	0.82 (0.74, 0.90)	0.88 (0.80, 0.95)
NPV, point estimate (95% CI)	0.88 (0.51, 1)	0.70 (0.39, 0.90)	0.74 (0.54, 0.93)
% pathology positive, point estimate (95% CI)	0.75 (0.66, 0.84)	0.76 (0.68, 0.85)	0.75 (0.66, 0.84)

Source: PyL 2301 (OSPREY) Clinical Study Report, Section 11.4.2.2 and Table 21, FDA clinical reviewer analysis (true negative, specificity, NPV, % pathology positive).
Abbreviations: CI = confidence interval, n = number of lesions, NPV = negative predictive value, PET = positron emission tomography, PPV = positive predictive value

8.1.6. Integrated Assessment of Effectiveness

The Applicant's data provide support for the effectiveness of piflufolastat F 18 for imaging of prostate cancer. However, weaknesses in the evidence must be considered when evaluating whether standards for effectiveness have been met.

In PyL 2301 (OSPREY) Cohort A, the major issue is the failure of all three independent readers to meet the prespecified threshold of 40% for sensitivity, with the lower bound of the 95% confidence interval ranging from 19% to 30% for the primary analysis and from 17% to 27% when region matching was used. However, specificity far exceeded the pre-specified threshold of 80% for all three readers both with and without region matching. It is important to note that current treatment guidelines incorporate imaging modalities with similar sensitivity, and a test with low sensitivity but high specificity can still provide clinical utility. Because definitive therapies for prostate cancer such as radical prostatectomy and radiotherapy are associated with significant morbidity, and because the presence of pelvic nodal metastases may make a patient less likely to benefit from these therapies, identification of pelvic nodal disease on PET could aid in avoiding futile therapy. While low sensitivity will decrease the number of patients who benefit, each individual patient with true positive results potentially adds diagnostic value. Conversely, patients with pelvic nodal metastasis that is missed by the PET scan will likely proceed to definitive therapy just as they would have with no PET scan at all.

In this clinical setting of primary prostate cancer, a relevant statistic is PPV, which ideally would be high enough to avoid additional confirmatory testing of positive results. In PyL 2301 (OSPREY) Cohort A, PPV ranged from 64% to 70% at the lower bound of the 95% confidence interval for the primary analysis and 56% to 62% when region matching was used. While literature estimates of prevalence of pelvic lymph node metastasis vary somewhat, one study reported a rate of 23% for NCCN high risk patients and 47% for NCCN very high risk patients (Reichard et al., 2021). The PPV results seen in PyL 2301 (OSPREY) are well above these estimates, demonstrating added value of the PET scan. Also, since PPV is dependent upon prevalence of metastasis in the intended patient population, performance would be expected to improve in patients with higher suspicion of metastasis (i.e., those of higher risk stratification). In support of this concept, there was a trend towards more true positive results among patients with higher T stage or higher Gleason score, well-established risk markers.

The type of initial definitive therapy in PyL 2301 (OSPREY) Cohort A was limited to prostatectomy because this therapy is often accompanied by template pelvic lymph node dissection as standard-of-care, which allowed collection of histopathology data for the study. In clinical practice, other therapies, particularly external beam radiotherapy or brachytherapy, are often used. However, it is expected that the sensitivity and specificity of piflufolastat F 18 PET will be similar between patients who are candidates for radiotherapy and those who are candidates for surgery.

In PyL 3301 (CONDOR), there were weaknesses with the design of the composite reference standard. For feasibility reasons, central read results were not used to direct the collection of reference standard data; instead, local evaluation of the PET images guided collection of these data. Thus, lesions that were not identified by the local readers often could not be evaluated. For the imaging component of the reference standard, which comprised at least 70% of the useful data, the criteria for determining that a lesion represented prostate cancer were largely subjective. The reference standard readers also had access to the piflufolastat F 18 PET images, though they were blinded to the result of the central PET readers. In addition, the time for collection of follow up imaging was restricted to 60 days, limiting the use of change in size as a marker of disease. These issues, particularly the subjective reference standard imaging interpretation criteria and the availability of investigational PET images to reference standard readers, raise the possibility of biased reference standard image interpretation. However, use of two central reference standard image evaluators, although reading in consensus, may have limited this potential source of bias.

A non-trivial fraction of PET positive patients in PyL 3301 (CONDOR), 19% to 24% depending on reader, lacked reference standard data. This was partially due to discrepancy in PET results between the local and central readers, as discussed above. Subgroup analyses showed a trend to lower PSA level in the PET positive patients without reference standard results, raising the possibility that patient-level PPV performance was overestimated in this study. In addition, not all PET positive lesions were evaluated in the patients who did have reference standard results. Despite these issues, the study results are considered meaningful based on the relatively

limited number of patients who lacked reference standard information, the reasonable results observed in patients with low PSA level who had reference standard results, and statistical imputation and tipping point analyses described in Statistical Evaluation Section 8.3.2. Also note that for the above estimates of CDR, PET positive patients who lacked matching reference standard information were included only in the denominator, thus lowering results. See Section 8.3.2 for PPV and CDR analyses using various imputation approaches for PET positive patients who lacked reference standard data.

Exploratory analyses of region-level PPV in PyL 3301 (CONDOR) show lower estimates compared to patient-level PPV, 59% to 62% at the lower bound of the 95% confidence interval versus 78% to 80%, respectively. The difference between these values appears to be largely explained by evaluation of more than one region in some patients, as any true positive region defined a true positive patient. The region-level PPV remains reasonable with a lower bound greater than 50%, however, inclusion of region-level results in the label is warranted.

While the populations studied in the PyL 2301 (OSPREY) and PyL 3301 (CONDOR) trials were at different points in disease course, they shared the same type of cancer. Since the underlying mechanism of detecting metastasis is identical in these populations, the trials are considered mutually supportive. As an example, the ability of piflufolastat F 18 to detect extrapelvic metastatic disease prior to initial definitive therapy of prostate cancer was not assessed against a reference standard in Cohort A of PyL 2301 (OSPREY). However, the ability to detect distant metastases in this population can be reasonably extrapolated from the performance of the investigational drug in detecting bone and extrapelvic soft tissue metastases in PyL 3301 (CONDOR), and is further supported by the results of PyL 2301 (OSPREY) Cohort B.

After considering the above issues, we find that the Applicant has submitted sufficient evidence of effectiveness, in the form of two adequate and well-controlled trials with additional supportive evidence, to meet the regulatory standards for approval. (b) (4)

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data were collected in both PyL 2301 (OSPREY) and PyL 3301 (CONDOR), as well as the J17149 urinalysis trial (Table 7), and all of these data sources were reviewed. PyL 2301 (OSPREY) provided the bulk of the safety laboratory and ECG results.

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

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant pooled results from PyL 2301 (OSPREY) and PyL 3301 (CONDOR) for most safety analyses. This is a reasonable strategy as both trials enrolled patients with prostate cancer and the differences between disease status, i.e. primary versus recurrent cancer, are not expected to impact safety. In addition, the trials used very similar doses of piflufolastat F 18 and each patient received a single dose. While the adverse event (AE) follow up differed slightly between the trials, both included a sufficient length of follow up. The J17149 study was not included in the pooled safety data given its small size, shorter duration of AE monitoring of 24 hours, and absence of treatment emergent AE reports. This pooling approach for safety data was discussed at the pre-NDA meeting and agreement between the Applicant and FDA was reached.

The pooled Safety Analysis Set contains 593 patients, defined as all patients enrolled in either PyL 2301 (OSPREY) or PyL 3301 (CONDOR) who received any amount of piflufolastat F 18. Each patient received a single dose of the investigational radiopharmaceutical, and as shown in Table 35, the mean dose was 9.2 mCi. This aligns with the Applicant's proposed target dose of 9 mCi in the draft prescribing information.

The safety population is predominantly white. However, we are not aware of data to suggest that race will influence likelihood or severity of AEs.

Table 35. Baseline characteristics of the pooled Safety Analysis Set

Parameters	Pooled Safety Set (n=593) n (%)	PyL 2301 (OSPREY) (n=385) n (%)	PyL 3301 (CONDOR) (n=208) n (%)
Age			
Mean years (SD)	66.2 (7.6)	65.2 (7.3)	67.9 (7.8)
Median (years)	66.0	66.0	68.0
Min, max (years)	43, 91	45 ,86	43, 91
Age Group			
< 65 years	238 (40%)	171 (44%)	67 (32%)
≥ 65 years	355 (60%)	214 (56%)	141 (68%)
Race			
White	522 (88%)	334 (87%)	188 (90%)
Black or African American	44 (7%)	29 (8%)	15 (7%)
Asian	14 (2%)	11 (3%)	3 (1%)
Other, including not reported	13 (2%)	11 (3%)	2 (1%)
Ethnicity			
Hispanic or Latino	21 (4%)	16 (4%)	5 (2%)
Not Hispanic or Latino	557 (94%)	361 (94%)	196 (94%)
Missing	15 (2%)	8 (2%)	7 (3%)
Dose			
Dose (mCi) (SD)	9.2 (0.7)	9.1 (0.7)	9.4 (0.7)

Source: Summary of Clinical Safety, Tables 2 and 3, PyL 2301 (OSPREY) Clinical Study Report, Tables 11 and 31, PyL 3301 (CONDOR) Clinical Study Report, Tables 5 and 21.
Abbreviations: max = maximum, min = minimum, n = number of patients, SD = standard deviation

Adequacy of the safety database:

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

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

In PyL 2301 (OSPREY), AE data were collected on the day of administration of the investigational drug and at the pre-surgery or pre-biopsy follow up visit, which was to occur within 28 days. Additional AE monitoring occurred for some patients by telephone call at 4 to 10 days post-dose if the surgery or biopsy had not occurred and at 14 to 28 days after any biopsy. AE severity was graded using CTCAE version 4.03, and AE relatedness was assessed by the investigator using a binary scale of related or unrelated. For analysis, AEs were coded using MedDRA version 19.1.

In PyL 3301 (CONDOR), AE recording began after injection of piflufolastat F 18. A follow up telephone call for AE surveillance was done at 4 to 10 days. AE severity and relatedness were assessed by the same criteria used in PyL 2301 (OSPREY). For analysis, AEs were coded using MedDRA version 21.1.

In the integrated AE analysis, events from PyL 2301 (OSPREY) were recoded to MedDRA version 21.1. If more than one event occurred per patient, that patient was counted once for each system organ class and preferred term. The coding of verbatim terms to lowest level terms was audited during the review and no substantial issues were found.

Routine Clinical Tests

In PyL 2301 (OSPREY), vital signs (temperature, respiratory rate, blood pressure, and heart rate) and ECG were collected twice on the day of dosing with piflufolastat F 18, prior to administration and following administration before imaging. While exact times for these assessments were not specified, the time between dosing and imaging was set as 1 to 2 hours. Safety laboratory samples (complete blood count with differential, comprehensive metabolic panel) were obtained at the screening and follow up visits. The protocol defined time between these visits was 1 to 58 days.

In PyL 3301 (CONDOR), vital signs (blood pressure and heart rate) were recorded twice on the day of dosing with piflufolastat F 18, before and after administration. ECG and safety laboratory data were not obtained.

In J17149, urine samples for urinalysis were collected prior to dosing with piflufolastat F 18 and approximately 24 hours afterwards.

The acquisition of ECG and safety laboratory data in a subset of the pooled Safety Set is reasonable, because the likelihood of a meaningful drug-induced effect on these values is low

given the microdose mass of the drug (varies, but on the order of 5 µg) and anticipated infrequent administration.

8.2.4. Safety Results

Deaths

No deaths were reported during the observation period.

Serious Adverse Events

A total of 10 serious adverse events (SAEs) were reported in 8 patients, as listed in Table 36. All but one event, hypersensitivity, were assessed as unrelated by the Applicant. Upon review of the narrative summaries for these events, this assessment appears appropriate. Atrial fibrillation, coronary artery disease, and lower gastrointestinal hemorrhage are relatively common in the older adult male population that was studied. Acute pyelonephritis is also not rare, and patients with prostate cancer may be at increased risk due to cancer- or treatment-related lower urinary tract changes. The patient with spinal cord compression was enrolled in PyL 2301 (OSPREY) Cohort B and had widespread osseous metastatic disease that was found during the trial to have progressed. The patient with hyperkalemia had acute on chronic renal insufficiency and mild hyperkalemia prior to administration of piflufolastat F 18 and was not compliant with bicarbonate therapy.

One patient (PYL-3301 (b) (6)) experienced SAEs of hypersensitivity, headache, and paresthesia. This 74-year-old had biochemically recurrent prostate cancer after initial treatment with radical prostatectomy and pelvic lymph node dissection. Other potentially relevant medical history included multiple drug and food allergies, including to gadolinium-based contrast and iodinated contrast, trigeminal neuralgia, diabetes, and anxiety disorder. One day after administration of 9.3 mCi piflufolastat F 18, he began to note fatigue, dyspnea, chest pressure, a sense of oropharyngeal constriction, a sense of glossal edema, itchy eyes, head pressure, and dizziness. The symptoms worsened, and the next day he presented to the emergency department where he was diagnosed with a grade 3 allergic reaction and treated with multiple drugs, including a steroid and antihistamines. The next day, the event was considered resolved and he was discharged home. Three days post-discharge (6 days after dosing with piflufolastat F 18), the patient developed right-sided headache, right facial pain, and numbness and paresthesia of the left arm. These events were reported to study staff the next day at follow up, and subsequently he presented to the emergency department. After evaluation, the differential diagnosis included trigeminal neuralgia with a low suspicion of temporal arteritis. The events of headache and paresthesia were considered resolved that day. Based on this information, along with additional details in the full narrative, the Applicant's assessments that the event of allergy may be related to the investigational drug and that the events of headache and paresthesia are unrelated appear reasonable.

Table 36. Listing of serious adverse events in the pooled Safety Analysis Set

MedDRA SOC or PT	Pooled Safety Set (n=593) n (%)
Cardiac disorders	3 (0.5%)
Atrial fibrillation	1 (0.2%)
Coronary artery disease	2 (0.3%)
Gastrointestinal disorders	1 (0.2%)
Lower gastrointestinal hemorrhage	1 (0.2%)
Immune system disorders	1 (0.2%)
Hypersensitivity	1 (0.2%)
Infections and infestations	1 (0.2%)
Pyelonephritis acute	1 (0.2%)
Metabolism and nutrition disorders	1 (0.2%)
Hyperkalemia	1 (0.2%)
Nervous system disorders	2 (0.3%)
Headache	1 (0.2%)
Paresthesia	1 (0.2%)
Spinal cord compression	1 (0.2%)

Source: Summary of Clinical Safety, Table 9.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients, PT = preferred term, SOC = system organ class
Note: The numbers in this table refer to patients not events.

Dropouts and/or Discontinuations Due to Adverse Effects

No study dropouts or discontinuations due to AEs were reported.

Significant Adverse Events

Other than the above described SAE of allergy, no significant AEs were reported.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 102 treatment-emergent AEs were reported in 65 (11%) of the 593 patients in the pooled Safety Set, including the SAEs listed in Table 36. Events that occurred in more than one patient are shown in Table 37. The most common adverse events were headache, dysgeusia, and fatigue. Severity of the adverse events was most often mild (CTCAE grade 1), as reported in 51 (78%) of 65 patients. Nine events in six patients were considered severe (CTCAE grade 3). These included two events of headache and one event each of paresthesia, spinal cord

compression, lower gastrointestinal hemorrhage, pseudomonal urinary tract infection, coronary artery disease, hyperkalemia, and hypersensitivity.

Table 37. Listing of treatment-emergent adverse events occurring in more than one patient

MedDRA SOC or PT	Pooled Safety Set (n=593) n (%)
Any event	65 (11.0%)
Nervous system disorders	
Headache	13 (2.2%)
Dysgeusia	10 (1.7%)
General disorders and administration site conditions	
Fatigue	7 (1.2%)
Gastrointestinal disorders	
Diarrhea	3 (0.5%)
Infections and infestations	
Upper respiratory tract infection	2 (0.3%)
Musculoskeletal and connective tissue disorders	
Arthralgia	2 (0.3%)
Skin and subcutaneous tissue disorders	
Rash	2 (0.3%)
Cardiac disorders	
Coronary artery disease	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	
Epistaxis	2 (0.3%)
Investigations	
Alanine aminotransferase increased	2 (0.3%)
Vascular disorders	
Hypertension	2 (0.3%)

Source: Summary of Clinical Safety, Table 5.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients, PT = preferred term, SOC = system organ class

Events assessed as related to the investigational drug were reported in 30 patients. These events are listed in Table 38.

Table 38. Listing of treatment-emergent adverse events assessed as related to drug exposure

MedDRA PT	Pooled Safety Set (n=593) n (%)
Any related event	30 (5.1%)
Headache	9 (1.5%)
Dysgeusia	8 (1.3%)
Fatigue	4 (0.7%)
Dizziness	1 (0.2%)
Hyperesthesia	1 (0.2%)
Migraine	1 (0.2%)
Visual field defect	1 (0.2%)
Application site rash	1 (0.2%)
Chest discomfort	1 (0.2%)
Feeling abnormal	1 (0.2%)
Injection site pain	1 (0.2%)

Arthralgia	1 (0.2%)
Muscular weakness	1 (0.2%)
Pain in extremity	1 (0.2%)
Rash	1 (0.2%)
Dry skin	1 (0.2%)
Rash generalized	1 (0.2%)
Dehydration	1 (0.2%)
Dysuria	1 (0.2%)
Vertigo	1 (0.2%)
Hypersensitivity	1 (0.2%)
Disorientation	1 (0.2%)

Source: Summary of Clinical Safety, Table 7.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, n = number of patients, PT = preferred term

The Applicant proposes to include headache, dysgeusia, and fatigue in the prescribing information as the most frequent adverse reactions. They also propose to state that hypersensitivity was observed in one patient with a significant history of adverse reactions. This approach is reasonable based on the collected AE data.

Laboratory Findings

Laboratory findings were evaluated by descriptive statistics, shift tables, and examination of results in patients flagged by the Applicant as having clinically significant abnormalities. In addition, JMP Clinical version 7.1 was used to screen for potential Hy's Law cases, and none were found.

The Applicant did not predefine criteria for clinical significance in regard to laboratory abnormalities. They state that values were generally considered clinically relevant if they were grade 3 or 4, serious, or led to study discontinuation. A total of 14 laboratory abnormalities were listed as clinically significant in 10 patients at follow up and 9 laboratory abnormalities in 7 patients at baseline. The clinically significant results for patients with at least one laboratory abnormality listed as clinically significant at follow up but not at baseline are shown in Table 39. Hyperkalemia in patient (b) (6) was considered a SAE as described above. The significance of elevated glucose and triglyceride levels is difficult to determine as both normal ranges assume fasting. While one patient (b) (6)) was found to have new increases in AST and ALT 7 days after receiving piflufolastat F 18, the other two patients with clinically significant follow up AST and/or ALT levels decreased from the pretreatment baseline levels.

Table 39. Laboratory results for patients with at least one new clinically significant abnormality at follow up

Patient	Laboratory	Baseline Value	Follow Up Value	Normal Range
(b) (6)	Potassium (mmol/L)	5.5*	7.2	3.3-5
	Glucose (mmol/L)	5.55*	8.769	3.885-5.495
	ALT (ukat/L)	2.305*	1.470	0.084-0.618
	ALT (ukat/L)	1.804**	1.687	0.2-1.002
	AST (ukat/L)	1.804**	1.653	0.284-0.701

	Bilirubin (umol/L)	18.8144	30.787	3.421-22.235
(b) (6)	Triglycerides (mmol/L)	ND	78.78	≤1.7
	ALT (ukat/L)	0.4175	1.653	≤0.835
	AST (ukat/L)	0.5845	1.136	≤0.668

Source: PyL 2301 (OSPREY) Clinical Study Report, Table 14.3.4-2, ADLB.xpt.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ND = not determined
* = This result is outside the normal range but was not listed as clinically significant, ** = This baseline result was listed as clinically significant

Laboratory results showing imbalances in shifts after piflufolastat F 18 in at least 10 patients are shown in Table 40. There were slight shift imbalances toward lower levels of hemoglobin, hematocrit, and erythrocyte count, all of which would be compatible with anemia. However, anemia is a relatively common issue in the studied patient population. Another confounding factor that also affects assessment of bilirubin and calcium levels is the variable and potentially long time span between baseline and follow up laboratory measurements. For example, both the mean and median time between baseline and follow up calcium levels was 21 days. A causative role of the piflufolastat F 18 for any of the observed laboratory abnormalities is considered unlikely due to the administration of a single, low mass dose, and lack of biologically plausible mechanism.

Table 40. Shift table for selected laboratory results

Laboratory	Shift	Change, mean (SD)	Change, range	Total n Evaluable
Bilirubin (mg/dL)	24 normal to high	0.64 (0.30)	0.12 – 1.20	302
	6 high to normal	-0.53 (0.21)	-0.29 – -0.80	
Calcium (mg/dL)	26 normal to low	-0.99 (0.49)	-0.10 – -1.90	332
	1 low to normal	0.40		
Hematocrit (%)	30 normal to low	-3.7 (2.5)	-0.1 – -9.5	337
	18 low to normal	2.5 (1.5)	0.2 – 5.7	
Hemoglobin (g/dL)	19 normal to low	-1.6 (0.9)	-0.3 – -3.2	337
	9 low to normal	1.0 (0.3)	0.6 – 1.7	
Erythrocytes ($x10^{12}$/L)	26 normal to low	-0.41 (0.27)	-0.04 – -0.96	337
	9 low to normal	0.33 (0.18)	0.12 – 0.70	

Source: Adapted from PyL 2301 (OSPREY) Clinical Study Report, Tables 14.3.6-1, 14.3.6-2, and 14.3.6-3.
Abbreviations: n = number of patients, SD = standard deviation

Vital Signs

Assessment of vital sign data was by descriptive statistics, shift table, correlation of changes in vital signs to piflufolastat F 18 dose, and examination of results for patients with the largest changes. No findings were identified to suggest a meaningful effect of the drug on blood pressure, temperature, or respiration rate. As seen in Table 41, there may be a mild imbalance in shifts to lower heart rate after administration. The average change in heart rate (post-pre) was -4 bpm with a standard deviation of 7 bpm, and the average absolute value of change in heart rate was 6 ± 5 bpm. No patients were reported to have heart rate outside the range of 40 to 130 after piflufolastat F 18 was administered. Because of the small magnitude of the

observed effect, the low mass dose of the drug, and the lack of a biologically plausible explanation for an effect on heart rate, it is considered likely that the observed shift represents either a physiologic response to resting during the PET scan or statistical variation.

Table 41. Shift table for heart rate before and after administration of piflufolastat F 18

Pre-PET Heart Rate	Post-PET Heart Rate	n (%) (n=580)
Normal		
	Bradycardia	89 (15%)
	Normal	371 (64%)
	Tachycardia	1 (<1%)
Bradycardia		
	Bradycardia	95 (16%)
	Normal	13 (2%)
Severe bradycardia		
	Bradycardia	1 (<1%)
Tachycardia		
	Normal	10 (2%)

Source: FDA clinical reviewer analysis.
Abbreviations: bpm = beats per minute, n = number of patients, PET = positron emission tomography
Note: For this analysis, normal heart rate is considered 60-100 bpm, bradycardia is 40-59 bpm, severe bradycardia is <40 bpm, and tachycardia is 101-130 bpm.

Electrocardiograms (ECGs)

Per protocol, the onsite Investigators were responsible for evaluation of ECGs. The Applicant states that no patient had ECG results classified as abnormal and clinically significant either before or after administration of piflufolastat F 18. The QTcF increased an average of 2.1 msec after administration of the investigational drug, with a standard deviation of 10 msec. A total of 3 (0.8%) of 372 patients had an increase in QTcF of more than 30 msec and no patients had an increase of more than 60 msec.

QT

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

Immunogenicity

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

8.2.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified.

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

COA data were not collected and were not needed.

8.2.7. Safety Analyses by Demographic Subgroups

As seen in Table 42, patients with AEs who were younger than 65 years old were slightly overrepresented compared to the age distribution in the combined Safety Set. This finding is very unlikely to be clinically relevant. Due to the relatively low AE rate, meaningful subgroup analyses for race or ethnicity were not feasible. Only males were enrolled, so subgroup analysis by sex was not done.

Table 42. Adverse events stratified by patient age

Reported Events	Age < 65	Age ≥ 65
Patients (n, % of total)	238 (40%)	355 (60%)
Adverse events (n, % of total)	48 (47%)	54 (53%)
Patients with adverse events (n, % of total)	31 (48%)	34 (52%)

Source: Integrated Summary of Safety, Table 2.9.1 and FDA clinical reviewer analysis (Adverse events row).
Abbreviations: n = number of patients or events

The median decay-corrected administered dose of piflufolastat F 18 among the combined Safety Set was 0.1031 mCi/kg. Using this value as a threshold, no dose-related increase in adverse event rate was observed (Table 43).

Table 43. Adverse events stratified by administered dose of piflufolastat F 18

Reported Events	Dose <0.1031 mCi/kg	Dose ≥ 0.1031 mCi/kg
Patients (n, % of total)	297 (50%)	296 (50%)
Adverse events (n, % of total)	59 (58%)	43 (42%)
Patients with adverse events (n, % of total)	38 (58%)	27 (42%)

Source: FDA clinical reviewer analysis.
Abbreviations: n = number of patients or events

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

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

Human Reproduction and Pregnancy

Piflufolastat F 18 is not intended for use in females.

Pediatrics and Assessment of Effects on Growth

Piflufolastat F 18 is not intended for use in children. A pediatric study waiver was granted as proposed in the agreed initial pediatric study plan letter of October 11, 2019, filed to IND 129952.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The maximum dose administered to a patient in the combined Safety Set was 11.07 mCi, and no large overdose was described by the Applicant during the drug development program. In the absence of clinical experience to guide management of overdose, it is reasonable to recommend increasing drug clearance by hydration and, if clinically feasible, by administration of a diuretic. The main goal of such measures is to reduce patient radiation exposure. As for any overdose involving radioactive materials, the radiation effective dose to the patient should be estimated if possible. See Section 11 of this review for related labeling recommendations.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Approved Ga 68 PSMA-11 injection shares a mechanism of action and some structural features with piflufolastat F 18. No safety signal has been identified from current postmarket experience with Ga 68 PSMA-11. In addition, an FDA review of the published literature did not reveal a safety signal from investigational or foreign use of piflufolastat F 18.

Expectations on Safety in the Postmarket Setting

While related to suboptimal efficacy rather than a direct drug safety issue, false positive and false negative results could adversely affect patient management. See Section 11 of this review for related labeling recommendations that address this risk. Specialized reader training beyond that of typical practicing nuclear medicine physicians does not seem required for interpretation of piflufolastat F 18 PET.

8.2.10. Integrated Assessment of Safety

A serious adverse reaction of hypersensitivity was experienced by one patient in the drug development program. This risk theoretically exists for essentially all drugs, and based on the observed incidence and the likely heightened sensitivity in the patient who experienced the reaction, the risk should be manageable through appropriate labeling. Overall, the observed safety profile was reasonably benign. Radiation exposure from piflufolastat F 18 is of a similar magnitude as other oncology PET drugs and is expected to result in low additional risk. Risk of misdiagnosis is another issue that will be addressed primarily through labeling, as discussed further in Section 11 of this review.

8.3. Statistical Evaluation

This NDA submission includes two adequate and well-controlled trials that assessed the diagnostic efficacy and safety of piflufolastat F18 PET in prostate cancer patients, PyL2301 (OSPREY) and PyL3301 (CONDOR). (b) (4)

8.3.1. Study PyL2301 (OSPREY) – Cohort A

Study PyL2301 (OSPREY) was conducted to evaluate the diagnostic performance of piflufolastat F 18 PET imaging in two prostate cancer patient populations: patients with high risk prostate cancer planned for surgery as initial definitive therapy (Cohort A), and patients with presumptive radiologic evidence on conventional imaging of recurrent or metastatic prostate cancer that was feasible for biopsy (Cohort B). This section covers FDA's statistical assessment of Cohort A.

Cohort A was a prospective multi-center, multi-reader, open-label, single-arm, non-randomized, single-dose clinical study. A total of 268 patients were enrolled. The Applicant considered 252 patients as the Evaluable Set for the primary analysis, excluding the remaining 16 patients who received piflufolastat F 18 PET imaging but did not have histopathology data collected. FDA clinical assessment of Cohort A of Study PyL2301 can be found in Sections 8.1.1 and 8.1.2.

The diagnostic performance of piflufolastat F 18 PET in the Evaluable Set for the co-primary efficacy endpoints reported by the Applicant was confirmed by the FDA statistical reviewer. The results for specificity reached statistical significance, with the lower limit of the 95% CIs of all three readers exceeding the success criterion of 80%. However, the results for sensitivity did not reach statistical significance as the lower bound of the 95% CIs (19% to 30%) did not exceed the pre-specified success criterion of 40% for all three readers (Table 12, Table 13).

One of the post-hoc sensitivity analyses of the co-primary endpoints excluded patients (n=27) with pathologic lesions $\leq$ 5 mm in metastatic foci size. Per the Applicant, this analysis was meant to account for the intrinsic detection limits of PET scanners for small lymph node metastases. In this analysis, piflufolastat F 18 PET demonstrated equally high specificity as in the primary analysis; further, sensitivity met the success criteria whereby the lower limit of the 95% CI exceeded 40% for the same two readers (Reader 1 and Reader 3) who rejected the null hypothesis for specificity. However, the clinical review team has serious concerns regarding the utility of this analysis, since the clinical relevance of estimating performance only for larger metastases is unclear.

To assess the impact on performance, a tipping point analysis was carried out (Table 44) in the 268 enrolled patients (referred to hereafter as the Intent-To-Image Set) such that the 16 patients without pelvic lymph node histopathology data had their results imputed as positive for prostate cancer with probability p ($p = 0, 0.25, 0.5, 0.75, 1$; where $p = 0$ means no histopathology results were imputed as positive for prostate cancer and $p = 1$ means all histopathology results were imputed as positive for prostate cancer).

Table 44. Tipping point analysis of piflufolastat F 18 performance for detection of pelvic lymph node metastases in the Intent-To-Image Set (OSPREY Cohort A)

Parameter		Reader 1 (n=268)	Reader 2 (n=268)	Reader 3 (n=268)
$p = 0$	TP	23	17	23
	FP	15	10	16
	FN	36	43	37
	TN	194	198	192
	Sensitivity (95% CI)	39 (27, 53)	28 (17, 41)	38 (26, 52)
	Specificity (95% CI)	93 (88, 96)	95 (91, 98)	92 (88, 96)
	PPV (95% CI)	61 (43, 76)	63 (42, 81)	59 (42, 74)
	NPV (95% CI)	84 (79, 89)	82 (77, 87)	84 (78, 88)
$p = 0.25$	TP	25	19	25
	FP	13	8	14
	FN	40	48	38
	TN	190	193	191
	Sensitivity (95% CI)	38 (27, 51)	28 (18, 41)	40 (28, 53)
	Specificity (95% CI)	94 (89, 97)	96 (92, 98)	93 (89, 96)
	PPV (95% CI)	66 (49, 80)	70 (50, 86)	64 (47, 79)
	NPV (95% CI)	83 (77, 87)	80 (74, 85)	83 (78, 88)
$p = 0.5$	TP	28	20	27
	FP	10	7	12
	FN	41	50	40
	TN	189	191	189
	Sensitivity (95% CI)	41 (29, 53)	29 (18, 41)	40 (28, 53)
	Specificity (95% CI)	95 (91, 98)	96 (93, 99)	94 (90, 97)
	PPV (95% CI)	74 (57, 87)	74 (54, 89)	69 (52, 83)
	NPV (95% CI)	82 (77, 87)	79 (74, 84)	83 (77, 87)
$p = 0.75$	TP	29	21	28
	FP	9	6	11
	FN	40	48	45
	TN	190	193	184
	Sensitivity (95% CI)	42 (30, 55)	30 (20, 43)	38 (27, 50)
	Specificity (95% CI)	95 (92, 98)	97 (94, 99)	94 (90, 97)

	PPV (95% CI)	76 (60, 89)	78 (58, 91)	72 (55, 85)
	NPV (95% CI)	83 (77, 87)	80 (74, 85)	80 (75, 85)
$p = 1$	TP	31	23	30
	FP	7	4	9
	FN	44	53	46
	TN	186	188	183
	Sensitivity (95% CI)	41 (30, 53)	30 (20, 42)	39 (28, 51)
	Specificity (95% CI)	96 (93, 99)	98 (95, 99)	95 (91, 98)
	PPV (95% CI)	82 (66, 92)	85 (66, 96)	77 (61, 89)
	NPV (95% CI)	81 (75, 86)	78 (72, 83)	80 (74, 85)

Source: FDA statistical reviewer analysis
Note: interval estimates are based on Clopper-Pearson method;
p = the imputed probability of histopathology results positive for prostate cancer in the 16 patients without pelvic lymph node histopathology data

A refined imputation that incorporated patient-specific factors including baseline tumor stage, baseline Gleason score, and baseline PSA was performed in the Intent-To-Image Set. Two patients ((b) (6)) were imputed with 0.75 probability of pelvic lymph node histopathology positive for prostate cancer because they had bone biopsies positive for distant metastatic disease and were therefore considered at higher risk for pelvic lymph node metastases. Following discussion with the clinical team, the remaining patients without reference standard information were imputed with 0.5 probability of pelvic lymph node histopathology positive for prostate cancer if they were categorized as very high risk by NCCN criteria and with 0.25 probability of pelvic lymph node histopathology positive for prostate cancer if they were categorized as high risk by NCCN criteria. The results of this refined imputation are presented side-by-side with the Evaluable Set results in Table 45.

Table 45: Refined imputation analysis results of piflufolastat F 18 for detection of pelvic lymph node metastases in the Intent-To-Image Set compared to Evaluable Set results (OSPREY Cohort A)

Parameter	Reader 1		Reader 2		Reader 3	
	Eval (n=252)	ITT (n=268)	Eval (n=252)	ITT (n=268)	Eval (n=252)	ITT (n=268)
TP	23	27.25	17	20	23	26.75
FP	7	10.75	4	7	9	12.25
FN	36	38.75	43	47	37	40.25
TN	186	191.25	188	194	183	188.75
Sensitivity	39 (27, 53)	41 (29, 54)	28 (17, 41)	30 (19, 42)	38 (26, 52)	40 (28, 53)
Specificity	96 (93, 99)	95 (91, 97)	98 (95, 99)	97 (93, 99)	95 (91, 98)	94 (90, 97)
PPV	77 (58, 90)	72 (55, 85)	81 (58, 95)	74 (54, 89)	72 (53, 86)	69 (52, 82)
NPV	84 (78, 88)	83 (78, 88)	81 (76, 86)	80 (75, 85)	83 (78, 88)	82 (77, 87)

Source: FDA statistical reviewer analysis.
Footnote: Clopper-Pearson confidence intervals are reported
Eval = Evaluable Set results without imputation

ITT = Intent-To-Image Set results using a refined analysis in which the 16 patients without pelvic lymph node histopathology were imputed with a probability of histopathology results positive for prostate cancer of 0.75 in the setting of bone biopsies positive for distant metastatic disease, 0.5 if categorized as very high risk by NCCN criteria, and 0.25 if categorized as high risk by NCCN criteria.

Compared to the Evaluable Set results (n=252), the Intent-To-Image Set results (n=268) that included the 16 patients whose probabilities of prostate cancer metastasis to the pelvic lymph nodes were imputed based on a refined approach showed slightly improved sensitivity, very similar specificity and NPV, and slightly decreased PPV; the point estimate of PPV decreased 3% to 7% with the lower bound of 95% confidence interval decreasing from 58% to 55% for reader 1, from 58% to 54% for reader 2 and from 53% to 52% for reader 3. Compared to the simple imputation probability of 0.5 for all patients without histopathology data shown in Table 44, the PPV estimates were 2% lower for reader 1, but essentially the same for reader 2 and reader 3 using the refined imputation approach.

The 23% of patients with pelvic lymph node histopathology positive for prostate cancer in OSPREY Cohort A is within the typical range reported in the literature, though estimates vary based on numerous risk factors as well as the extent of pelvic lymph node dissection (Liss et al., 2013; Heck et al., 2014; Batra et al., 2015; Reichard et al., 2021). Given the lowest limit of the 95% confidence interval for PPV across all readers was greater than 50% from either 50:50 imputation or refined imputation and was greater than 40% with the most conservative imputation of 0:100, piflufolastat F 18 PET is expected to add clinical value in light of estimates of the prevalence of pelvic lymph node metastasis in the intended patient population. The OSPREY Cohort A data further suggest that PPV would be expected to improve in patients with suspected metastasis, i.e., those of higher risk stratification.

8.3.2. Study PyL3301 (CONDOR)

Study PyL3301 was a prospective, multi-center, multi-reader, open-label, single-arm, non-randomized, single-dose clinical study. A total of 208 patients were enrolled and comprised the Full Analysis Set. The three readers generated different numbers of positive piflufolastat F 18 PET scan assessments (137, 124, and 123) and different numbers of evaluable patients (104, 100, and 99) for the primary efficacy analysis.

Distribution of baseline PSA

Table 46 shows the per reader distribution of patients without reference standard results by baseline PSA level and piflufolastat F 18 PET results. Among PET positive patients who had composite reference standard data collected, an increasing percentage of patients with increasing baseline PSA level was observed. In contrast, a reverse trend was observed in PET positive patients without reference standard data collected, which appeared to mimic baseline PSA distribution in PET negative patients, whose composite reference standard data were not systematically collected. The similarity of baseline PSA distribution between PET positive

patients with no composite reference standard data and PET negative patients and the difference of baseline PSA distribution between these two patient groups and PET positive patients with composite reference standard data might imply the potential of bias in selecting patients for composite reference standard data collection. Of note, a higher percentage of PET positive patients had baseline PSA missing in the group with no composite reference standard data (12% to 17% across the three readers) than in the group with composite reference standard data (1% to 2%).

Table 46. Per reader distribution of patients without reference standard results by baseline PSA level and piflufolastat F 18 PET results

PSA level (ng/ml)	PET+ patients with reference standard (% in total)			PET+ patients w/o reference standard (% in total)			PET- patients w/o reference standard (% in total)		
	R1	R2	R3	R1	R2	R3	R1	R2	R3
≤0.5	15 (14%)	13 (13%)	15 (15%)	14 (42%)	10 (42%)	10 (42%)	40 (56%)	46 (55%)	44 (52%)
0.5 to ≤1	16 (15%)	13 (13%)	15(15%)	5 (15%)	4 (17%)	4 (17%)	16 (23%)	20 (24%)	18 (21%)
1 to ≤2	20 (19%)	18 (18%)	18 (18%)	4(12%)	4 (17%)	1 (4%)	9 (13%)	11 (13%)	14 (16%)
2 to ≤5	23 (22%)	26 (26%)	22 (22%)	5(15%)	3 (13&)	5 (21%)	5 (7%)	4 (5%)	6 (7%)
>5	28 (27%)	29 (29%)	27 (27%)	1 (3%)	0	0	1 (1%)	1 (1%)	3 (4%)
missing	2 (2%)	1 (1%)	2 (2%)	4 (12%)	3 (13%)	4 (17%)	0	2 (2%)	0
Total	104	100	99	33	24	24	71	84	85

Source: FDA statistical reviewer analysis
PET+: PET positive scan; PET-: PET negative scan.

Patient-level PPV

The primary efficacy endpoint was patient-level PPV (i.e., Applicant's CLR). As shown in Table 25 in Section 8.1.4, the Applicant reported patient-level PPV in the evaluable patients with composite reference standard information available as 85.6% (95% CI: 78.8%, 92.3%) for Reader 1, 87.0% (95% CI: 80.4%, 93.6%) for Reader 2, and 84.8% (95% CI: 77.8%, 91.9%) for Reader 3 based on the evaluable dataset. These results are termed PPVe in Table 47 and met the success criterion: the lower limit of the 95% CI of all three readers exceeded the threshold of 20%. Note that by definition, patient-level PPV should be estimated from all PET positive patients regardless of the availability of composite reference standard. In an analysis referred to as PPVi in Table 47, PET positive patients who lacked composite reference standard data in a PET positive region were all imputed as false positive, yielding patient-level PPV of 65% (95% CI: 57%, 73%) for Reader 1, 70% (95% CI: 62%, 78%) for Reader 2, and 68% (95% CI: 60%, 77%) for Reader 3.

A patient-level PPV tipping point analysis was performed with results also shown in Table 47. The lower bounds of 95% CI for patient-level PPV were 74%, 71% and 72% for Readers 1, 2, and 3 when imputing those without composite reference standard with 0.5 probability of being true

positive. This imputation assumes that composite reference standard data were lacking in a random fashion.

Table 47. Patient-level PPV and tipping point analysis results in CONDOR

	All Patients (n=208)		
	Reader 1	**Reader 2**	**Reader 3**
PET negative: n	71	84	85
PET positive: n	137	124	123
PET positive without reference standard: n	33	24	24
TP + FP: n	104	100	99
TP: n	89	87	84
FP: n	15	13	15
PPVi*: % (95% CI, %)	89/137, 65.0 (57.0, 73.0)	87/124, 70.2 (62.1, 78.2)	84/123, 68.3 (60.1, 76.5)
PPVe**: % (95% CI, %)	89/104, 85.6 (78.8, 92.3)	87/100, 87.0 (80.4, 93.6)	84/99, 84.8 (77.8, 91.9)
PPV Tipping Point Analysis[1]	N = 137	N = 124	N = 123
$p = 0.1$	93/137, 67.9 (60.1, 75.7)	89/124, 71.8 (63.9, 79.7)	89/123, 72.4 (64.5, 80.3)
$p = 0.2$	99/137, 72.3 (64.8, 79.8)	91/124, 73.4 (65.6, 81.2)	91/123, 74.0 (66.2, 81.7)
$p = 0.3$	104/137, 75.9 (68.8, 83.1)	93/124, 75.0 (67.4, 82.6)	92/123, 74.8 (67.1, 82.5)
$p = 0.4$	107/137, 78.1 (71.2, 85.0)	94/124, 75.8 (68.3, 83.3)	94/123, 76.4 (68.9, 83.9)
$p = 0.5$	110/137, 80.3 (73.6, 87.0)	97/124, 78.2 (71.0, 85.5)	97/123, 78.9 (71.6, 86.1)
$p = 0.6$	104/137, 75.9 (68.8, 83.1)	104/124, 83.9 (77.4, 90.3)	98/123, 79.7 (72.6, 86.8)
$p = 0.7$	107/137, 78.1 (71.2, 85.0)	105/124, 84.7 (78.3, 91.0)	100/123, 81.3 (74.4, 88.2)
$p = 0.8$	112/137, 81.8 (75.3, 88.2)	107/124, 86.3 (80.2, 92.3)	101/123, 82.1 (75.3, 88.9)
$p = 0.9$	118/137, 86.1 (80.3, 91.9)	109/124, 87.9 (82.2, 93.6)	103/123, 83.7 (77.2, 90.3)
$p = 1$	122/137, 89.1 (83.8, 94.3)	111/124, 89.5 (84.1, 94.9)	108/123, 87.8 (82.0, 93.6)

Source: FDA statistical reviewer analysis

*PPVi: positive predictive value in all PET positive patients (patients without composite reference standard data in a PET positive region were imputed as false positive)

**PPVe: positive predictive value in evaluable PET positive patients (patients without composite reference standard data in a PET positive region were excluded)

[1]PPV Tipping Point Analysis: PET positive patients without composite reference standard data in a PET positive region were imputed as positive with probability p (when $p = 0.1$, 10% of patients without composite reference standard data were imputed as true positive (equivalently, 90% of patients without composite reference standard data were imputed as false positive), and when $p = 1$, all PET positive patients without composite reference standard data were imputed as true positive).

A refined imputation analysis of patient-level PPV that incorporated patient-specific factors was performed for PET positive patients without composite reference standard data in a PET positive region. For each of these patients, the estimated likelihood that at least one PET positive lesion was truly prostate cancer was rated on a 3-point scale, based on patient-specific variables including total number of PET positive lesions and their regional distribution, size of the largest lesion, SUVmax of the most intense lesion, and baseline PSA. The rating was then

used to impute the probability of being true positive as 0.50, 0.55, or 0.60. The results of this refined patient-level PPV imputation (PPVi+) are presented in Table 48, along with PPVe, PPVi, and PPV with 50:50 imputation ($PPVi^{0.5}$) extracted from Table 47.

Table 48. Refined imputation analysis results and other analyses of patient-level PPV in CONDOR

	Reader 1	Reader 2	Reader 3
PPVe*: % (95% CI, %)	89/104, 85.6 (78.8, 92.3)	87/100, 87.0 (80.4, 93.6)	84/99, 84.8 (77.8, 91.9)
PPVi**: % (95% CI, %)	89/137, 65.0 (57.0, 73.0)	87/124, 70.2 (62.1, 78.2)	84/123, 68.3 (60.1, 76.5)
$PPVi^{0.5}$: % (95% CI, %)	110/137, 80.3 (73.6, 87.0)	97/124, 78.2 (71.0, 85.5)	97/123, 78.9 (71.6, 86.1)
PPVi+***: % (95% CI, %)	107/137, 78.1 (71.2, 85.0)	100.1/124, 80.7 (73.8, 87.7)	97.3/123, 79.1(71.9, 86.3)

Source: FDA statistical reviewer analysis

*PPVe: positive predictive value in evaluable PET positive patients (patients without composite reference standard data in a PET positive region were excluded)

**PPVi: positive predictive value in all PET positive patients (patients without composite reference standard data in a PET positive region were imputed as false positive)

$^{0.5}$PPVi: positive predictive value from the tipping point analysis in Table 47 where imputation probability p is 0.5

***PPVi+: positive predictive value in all PET positive patients with refined imputation based on patient-specific factors

The refined imputation in PET positive patients (PPVi+) without composite reference standard data (33, 24, and 24 patients by readers 1, 2, and 3, respectively) resulted in assignment of 18, 13.1, and 13.3 patients as true positive. As shown in Table 48, the lower bounds of the 95% CI of this refined imputed patient-level PPV increased to 71.2%, 73.8%, and 71.9%, as compared to 57%, 62.1%, and 60.1% for PPVi, which imputed all PET positive patients without composite reference standard as false positive. The refined imputation results were similar to the PPV tipping point analysis when 50:50 imputation probability was applied ($PPVi^{0.5}$). We note that there can be more than one valid way to perform imputation using patient-specific information in patients with no composite reference standard data. Given there was no pre-specified imputation approach, the above exploratory analyses demonstrate the impact on the primary efficacy results from a range of imputations including a tipping point analysis and a refined imputation approach.

The Applicant performed several sensitivity analyses of patient-level PPV. For example, multiple imputation (MI) assuming missing at random (MAR) and tipping point analyses (imputed 100 times) adjusting for pre-specified baseline covariates using the maximum likelihood estimates (MLE) were implemented (Table 49). The MLEs of patient-level PPV using MI and tipping point analysis were consistently higher than the primary endpoint analysis results using empirical estimates without adjusting for any covariates in the evaluable patients or all imaged patients. The MLEs of PPV obtained by re-running the SAS code provided by the Applicant was different by as much as 3.3% (89.7% versus 93.0% for the tipping point analysis, $\delta = -0.95$, Reader 3).

Table 49: Sensitivity analysis of patient-level PPV in all imaged patients in CONDOR using MI assuming MAR and using tipping point analysis: MLEs and empirical estimates

Parameter	Reader 1 (n=208)	Reader 2 (n=208)	Reader 3 (n=208)
Patients with negative scans, n (%)	71 (34.1)	84 (40.4)	85(40.9)
Patients with positive unevaluable scans, n (%)	33 (15.9)	24 (11.5)	24 (11.5)
Patients with scans rated negative by at least 1 reader and positive by at least 1 reader, n	16	29	30
Patients without composite reference standard response[1], n	38	38	38
Positive evaluable scan by central reader, n (%)	104 (50.0)	100 (48.1)	99 (47.6)
MI assuming MAR[2], n[3]	137	124	123
PPV, pooled result of MLE estimates in % and (95% CI, in %)[4]	95.9 (88.8, 100)	97.6 (92.2, 100)	94.4 (85.4, 100)
Reviewer analysis by re-running the SAS codes* 'adzpmi.v2.1.sas'	96.2 (89.2, 100)	97.7 (92.5, 100)	94.8 (86.2, 100)
Tipping point analysis[5]			
$\delta = -0.95$			
PPV pooled result of the MLE estimates in % and (95% CI, in %)[4]	88.5 (77.3, 99.6)	91.9 (82.4, 100)	89.7 (78.5, 100)
Reviewer analysis by re-ran the SAS codes* 'adzpmi.v2.1.sas'	91.3 (82.1, 100)	94.6 (87.4, 100)	93.0 (84.2, 100)
$\delta = -0.90$			
PPV pooled result of the MLE estimates in % and (95% CI, in %)[4]	88.7 (77.6, 99.8)	92.1 (82.6, 100)	89.8 (78.6, 100)
Reviewer analysis by re-ran the SAS codes* 'adzpmi.v2.1.sas'	91.4 (82.2, 100)	94.6 (87.4, 100)	93.0 (84.2, 100)
$\delta = -0.05$			
PPV pooled result of the MLE estimates in % and (95% CI, in %)[4]	95.5 (87.7, 100)	97.1 (90.9, 100)	94.2 (85.0, 100)
Reviewer analysis by re-ran the SAS codes* 'adzpmi.v2.1.sas'	95.9 (89.2, 100)	97.3 (91.9, 100)	95.0 (87.0, 100)

Source: PyL3301 Study Report Table 12 and *FDA statistical reviewer analysis

Abbreviations: PPV = positive predictive value, MI = multiple imputation, MAR = missing at random, MLE = maximum likelihood estimates

[1]No response was provided by at least one reader.

[2]The pooled results from 100 imputed datasets for MI, adjusted for the covariates of baseline age, prior ADT therapy, prior surgery, prior RT, and baseline PSA. The analysis was based on all patients with at least one positive piflufolastat F 18 PET scan, including one patient with reference standard method of PSA levels.

[3]Includes all patients with scans rated positive by at least one reader.

[4]Two-sided 95% CI derived from a one-sample binomial distribution.

[5]Tipping point analysis was performed following the instructions described in Section 9.7.3.5.3 of PyL3301 Study Report.

Subgroup analyses of patient-level PPV by composite reference standard method, baseline PSA, imaging modality, history of prostate cancer treatment, history of ADT use, time of piflufolastat

F 18 PET scan after dosing, size of the largest lesion, SUVmax, age group, race, ethnicity, and study site were performed by the Applicant. Exploratory subgroup analyses were performed for the baseline covariates used for adjustment for MLEs in the MI analysis and tipping point analysis, i.e., age (< 65 versus ≥ 65 years), surgery (yes or no), radiotherapy (yes or no), ADT (yes or no), and baseline PSA (< 2.0 mg/ml versus ≥ 2.0 mg/ml). In addition, model-based subgroup analyses using MLE (logistic regression model with covariates of age, prior treatment (surgery, radiotherapy, ADT), and PSA) and empirical estimates for patient-level PPV were also explored. Results are shown in Table 50. The empirical estimates of subgroup patient-level PPV were all greater than the 20% success threshold, and consistent between subgroups except the PSA subgroups.

Table 50. Patient-level PPV subgroup analysis results for CONDOR

	All Patient (n=208)		
	Reader 1	**Reader 2**	**Reader 3**
PET negative: n	71	84	85
PET positive: n	137	124	123
PET positive without reference standard: n	33	24	24
TP + FP: n	104	100	99
TP: n	89	87	84
FP: n	15	13	15
PPV = TP/(TP + FP)			
PPVe[1]: % (95% CI, %)	89/104, 85.6 (78.8, 92.3)	87/100, 87.0 (80.4, 93.6)	84/99, 84.8 (77.8, 91.9)
PPVe[2]: % (95% CI, %)	87/104, 83.6 (61.7, 100)	83/100, 82.7 (57.1, 100)	77/99, 77.8 (50.9, 100)
Subgroup Analysis	N = 104	N = 100	N = 99
Age (<65 vs >=65 years)	21/25, 84.0 (69.6, 98.4)	21/25, 84.0 (69.6, 98.4)	19/24, 79.2 (62.9, 95.4)
Empirical	68/79, 86.1 (78.4, 93.7)	66/75, 88.0 (80.6, 95.4)	65/75, 86.7 (79.0, 94.4)
Age (<65 vs >=65 years)	17/25, 66.7 (10.6, 100)	17/25, 66.7 (10.6, 100)	16/24, 66.7 (10.4, 100)
MLE-Logistic	68/79, 85.8 (66.0, 100)	64/75, 84.8 (55.5, 100)	63/75, 83.4 (59.8, 100)
Surgery (Y vs N)	69/82, 84.1 (76.2, 92.1)	64/75, 85.3 (77.3, 93.3)	63/76, 82.9 (74.4, 91.4)
Empirical	20/22, 90.9 (78.9, 100)	23/25, 92.0 (81.4, 100)	21/23, 91.3 (79.8, 100)
Surgery (Y vs N)	62/82, 76.0 (45.9, 100)	54/75, 72.0 (35.0, 100)	51/76, 67.5 (32.0, 100)
MLE-Logistic	22/22, 100 (., .)*	25/25, 100 (., .)*	23/23, 100 (., .)*
RT (Y vs N)	59/68, 86.8 (78.7, 94.8)	57/65, 87.7 (79.7, 95.7)	56/64, 87.5 (79.4, 95.6)
Empirical	30/36, 83.3 (71.2, 95.5)	30/35, 85.7 (74.1, 97.3)	28/35, 80.0 (66.7, 93.3)
RT (Y vs N)	64/68, 93.5 (79.3, 100)	60/65, 92.1 (74.5, 100)	59/64, 91.6 (73.7, 100)
MLE-Logistic	36/36, 100 (100, 100)	35/35, 100.0 (99.9, 100)	35/35, 100.0 (., .)*
ADT (Y vs N)	33/36, 91.7 (82.6, 100)	30/32, 93.8 (85.4, 100)	27/30, 90.0 (79.3, 100)
Empirical	56/68, 82.4 (73.3, 91.4)	57/68, 83.8 (75.1, 92.6)	57/69, 82.6 (73.7, 91.6)
ADT (Y vs N)	24/36, 66.7 (11.1, 100)	21/32, 66.7 (11.2, 100)	20/30, 66.7 (10.9, 100)

MLE-Logistic	50/68, 73.4 (40.8, 100)	44/68, 65.4 (27.6, 100)	51/69, 73.7 (40.7, 100)
PSA (<2.0mg/mL vs ≥ 2.0mg/mL) Empirical	40/51, 78.4 (67.1, 89.7)	34/44, 77.3 (64.9, 89.7)	37/48, 77.1 (65.2, 89.0)
	48/51, 94.1 (87.7, 100)	52/55, 94.5 (88.5, 100)	46/49, 93.9 (87.2, 100)
TP/Missing PSA	1/2	1/1	1/2
PSA (<2.0mg/mL vs ≥ 2.0mg/mL) MLE-Logistic	34/51, 65.9 (27.5, 100)	29/44, 66.3 (24.1, 100)	26/48, 55.1 (12.8, 97.4)
	51/51, 100 (., .)*	55/55, 100 (., .)*	49/49, 100 (., .)*

Source: FDA statistical reviewer analysis
Abbreviations: PPV = positive predictive value, TP = true positive, FP = false positive, MLE = maximum likelihood estimates, RT = radiotherapy, ADT = androgen deprivation therapy, PSA = prostate-specific antigen
[1]Empirical estimate in evaluable patients
[2]MLE estimate using logistic regression model with covariates of [age (<65 vs ≥ 65 years), prior treatment (surgery, RT, ADT), and PSA (<2.0 mg/mL vs ≥ 2.0 mg/mL)] in which the number of TP results is predicted by the model and only includes patients who have composite reference standard data.
* 95% CI cannot be estimated since all values are in a single category (all 1, no 0), for example 22/22 for reader 1

Patient-level correct detection rate (CDR)

CDR is defined as number of true positive patients out of all imaged patients. As shown in Table 25 in Section 8.1.4, the lower limit of the 95% CI of the estimated CDRs were 36%, 35% and 34% for readers 1, 2 and 3; all exceeded a 20% threshold. Note that for these results, PET positive patients without composite reference standard data were counted as non-true positive by the CDR definition. Therefore, these results are the most conservative CDR estimates.

Given the lack of composite reference standard data in a PET positive region in more than 20% of the PET positive patients, a tipping point analysis was performed (Table 51) in which these patients were imputed as true positive with probability p ranging from 0 to 1 with an increment of 0.1 ($p = 0$ means none of the patients without reference standard information in a PET positive region were imputed as true positive while $p = 1$ means all patients without reference standard information in a PET positive region were imputed as true positive). CDR estimates were as high as 46.1%, 39.9%, 39.9% for readers 1, 2, 3, respectively, if 50:50 random imputation was applied; that is, a patient has a probability of 0.5 of being true positive.

Table 51. Patient-level CDR tipping point analysis in CONDOR

	All Patient (n=208)		
	Reader 1	**Reader 2**	**Reader 3**
PET negative: n	71	84	85
PET positive: n	137	124	123
PET positive without reference standard: n	33	24	24
TP + FP: n	104	100	99
TP: n	89	87	84
FP: n	15	13	15
TP + FP + PET neg: n	175	184	184

Tipping Point Analysis[1]	N = 208	N = 208	N = 208
p=0	89/208, 42.8 (36.1, 49.5)	87/208, 41.8 (35.1, 48.5)	84/208, 40.4 (33.7, 47.1)
p=0.1	93/208, 44.7 (38.0, 51.5)	89/208, 42.8 (36.1, 49.5)	89/208, 42.8 (36.1, 49.5)
p=0.2	99/208, 47.6 (40.8, 54.4)	91/208, 43.8 (37.0, 50.5)	91/208, 43.8 (37.0, 50.5)
p=0.3	104/208, 50.0 (43.2, 56.8)	93/208, 44.7 (38.0, 51.5)	92/208, 44.2 (37.5, 51.0)
p=0.4	107/208, 51.4 (44.7, 58.2)	94/208, 45.2 (38.4, 52.0)	94/208, 45.2 (38.4, 52.0)
p=0.5	110/208, 52.9 (46.1, 59.7)	97/208, 46.6 (39.9, 53.4)	97/208, 46.6 (39.9, 53.4)
p=0.6	104/208, 50.0 (43.2, 56.8)	104/208, 50.0 (43.2, 56.8)	98/208, 47.1 (40.3, 53.9)
p=0.7	107/208, 51.4 (44.7, 58.2)	105/208, 50.5 (43.7, 57.3)	100/208, 48.1 (41.3, 54.9)
p=0.8	112/208, 53.8 (47.1, 60.6)	107/208, 51.4 (44.7, 58.2)	101/208, 48.6 (41.8, 55.3)
p=0.9	118/208, 56.7 (50.0, 63.5)	109/208, 52.4 (45.6, 59.2)	103/208, 49.5 (42.7, 56.3)
p=1	122/208, 58.7 (52.0, 65.3)	111/208, 53.4 (46.6, 60.1)	108/208, 51.9 (45.1, 58.7)

Source: FDA statistical reviewer analyses

Abbreviations: CDR = correct detection rate, TP = true positive, FP= false positive

[1]Tipping Point Analysis: PET positive patients without composite reference standard data in a PET positive region were imputed to TP with probability p ranging from $p = 0$ (none of the patients with unavailable composite reference standard data were imputed as TP) to $p = 1$ (all patients with unavailable composite reference standard data were imputed as TP).

A refined imputation analysis of patient-level CDR that considered patient-specific factors for PET positive patients without reference standard data in a PET positive region was performed in the same fashion as for the refined PPV imputation analysis displayed above in Table 48. The results of this refined patient-level CDR imputation (CDR+) are presented in Table 52, along with patient-level CDR with all PET positive patients without composite reference standard data in a PET positive region imputed as non-true positive as well as patient-level CDR with 50:50 imputation extracted from the tipping point results in Table 51.

Table 52. Refined imputation analysis results and other analyses of patient-level CDR in CONDOR

	Reader 1	Reader 2	Reader 3
CDR: % (95% CI, %)	89/208, 42.8 (36.1, 49.5)	87/208, 41.8 (35.1, 48.5)	84/208, 40.4 (33.7, 47.1)
$CDR^{0.5}$: % (95% CI, %)	110/208, 52.9 (46.1, 59.7)	97/208, 46.6 (39.9, 53.4)	97/208, 46.6 (39.9, 53.4)
CDR+*: % (95% CI, %)	107/208, 51.4 (44.7, 58.2)	100.1/208, 48.1 (41.3, 54.9)	97.3/208, 46.8(40.0, 53.6)

Source: FDA statistical reviewer analysis

CDR = correct detection rate in which all PET positive patients without reference standard data in a PET positive region were imputed as false positive

[0.5]CDR: correct detection rate in which PET positive patients without composite reference standard data in a PET positive region were imputed as true positive with probability $p = 0.5$

*CDR+: correct detection rate in which PET positive patients without reference standard data in a PET positive region were imputed using a refined approach based on patient-specific factors

Further, MLEs and empirical estimates using MI assuming MAR were explored. The results are summarized in Table 53. We note that based on CDR definition, the MLEs of the MI assuming MAR and adjusting for baseline covariates were still high (93.1%, 91.2%, and 83.5%); in contrast, the empirical estimates of MI without baseline covariate adjustment were 55.0%, 50.9%, and 49.0% for readers 1, 2 and 3, respectively. It appeared that the results of model-

based subgroup analysis were heavily affected by the model used when compared with empirical estimates.

Table 53. Sensitivity analysis results of patient-level CDR in all imaged patients in CONDOR using MI assuming MAR: MLE and empirical estimate

Parameter	Reader 1 (n=208)	Reader 2 (n=208)	Reader 3 (n=208)
Patients with negative scans, n (%)	71 (34.1)	84 (40.4)	85(40.9)
Patients with positive unevaluable scans, n (%)	33 (15.9)	24 (11.5)	24 (11.5)
Positive evaluable scan by central reader, n (%)	104 (50.0)	100 (48.1)	99 (47.6)
MI assuming MAR[1], n*, CDR **, MLE[2], reviewer analysis^	93.1 (85.7, 100)	91.2 (82.4, 100)	83.5 (70.4, 96.5)
MI assuming MAR[1], n*, CDR **, empirical estimates[3], reviewer analysis^	55.0 (47.8, 62.2)	50.9 (43.9, 57.9)	49.0 (42.0, 56.0)

Source: PyL3301 Study Report Table 12 and ^FDA statistical reviewer analysis
Abbreviations: CDR = correct detection rate, MI = multiple imputation, MAR = missing at random, MLE = maximum likelihood estimates
Includes all patients imaged patients (n=208)
**CDR = True positive patients/all imaged patients: PET positive without reference standard data in a PET positive region were imputed via MI
[1]The pooled results from 100 imputed datasets for MI.
[2] MLE is adjusted for covariates (baseline age, prior ADT therapy, prior surgery, prior radiotherapy, and baseline PSA)
[3] Empirical estimates are obtained without any covariates adjustment.

We further explored subgroup analyses using MLE (logistic regression model with covariates of age, prior treatment (surgery, radiotherapy, ADT), and PSA) and empirical estimates based on the CDR endpoint in all imaged patients. The results are shown in Table 54. Most of the empirical estimates of subgroup CDRs were greater than a 20% success threshold, but were sometimes inconsistent between subgroups. The MLEs of subgroup CDR results were less than a 20% success threshold in some subgroups.

Table 54. Patient-level CDR subgroup analysis results for CONDOR

	All Patient (n=208)		
	Reader 1	**Reader 2**	**Reader 3**
PET negative: n	71	84	85
PET positive: n	137	124	123
PET positive without reference standard: n	33	24	24
TP + FP: n	104	100	99
TP: n	89	87	84
FP: n	15	13	15
CDR = TP/(all patients imaged)			

all patients imaged: n	N = 208	N = 208	N = 208
CDR[1]: % (95% CI, %)	89/208, 42.8 (36.1, 49.5)	87/208, 41.8 (35.1, 48.5)	84/208, 40.4 (33.7, 47.1)
CDR[2]: % (95% CI, %)	69/208, 33.0 (15.4, 50.7)	47/208, 22.5 (7.6, 37.4)	49/208, 23.5 (8.7, 38.2)
Subgroup Analysis			
Age (<65 vs >=65 years) Empirical	21/67, 31.3 (20.2, 42.5)	21/67, 31.3 (20.2, 42.5)	19/67, 28.4 (17.6, 39.2)
	68/141, 48.2 (40.0, 56.5)	66/141, 46.8 (38.6, 55.0)	65/141, 46.1 (37.9, 54.3)
Age (<65 vs >=65 years)	11/67, 16.7 (0.0, 35.7)	11/67, 16.7 (0.0, 35.7)	11/67, 16.0 (0.0, 34.4)
	83/141, 58.8 (37.0, 80.7)	49/141, 35.0 (13.3, 56.8)	58/141, 41.0 (20.0, 62.0)
Surgery (Y vs N) Empirical	69/180, 38.3 (31.2, 45.4)	64/180, 35.6 (28.6, 42.5)	63/180, 35.0 (28.0, 42.0)
	20/28, 71.4 (54.7, 88.2)	23/28, 82.1 (68.0, 96.3)	21/28, 75.0 (59.0, 91.0)
MLE- (9.0, 42.5)	31/180, 17.2 (3.8, 30.5)	33/180, 18.5 (4.8, 32.3)	
	28/28, 100 (100, 100)	28/28, 100 (100, 100)	28/28, 100 (99.9, 100)
RT (Y vs N) Empirical	59/104, 56.7 (47.2, 66.3)	57/104, 54.8 (45.2, 64.4)	56/104, 53.8 (44.3, 63.4)
	30/104, 28.8 (20.1, 37.6)	30/104, 28.8 (20.1, 37.6)	28/104, 26.9 (18.4, 35.4)
RT (Y vs N) MLE-Logistic	43/	33/104, 31.4 (11.0, 51.7)	31/104, 30.2 (11.0, 49.4)
	18/104, 17.0 (0.0, 43.8)	14/104, 13.5 (0.0, 36.5)	8/104, 7.5 (0.0, 21.2)
ADT (Y vs N) Empirical	33/55, 60.0 (47.1, 72.9)	30/55, 54.5 (41.4, 67.7)	27/55, 49.1 (35.9, 62.3)
	56/153, 36.6 (29.0, 44.2)	57/153, 37.3 (29.6, 44.9)	57/153, 37.3 (29.6, 44.9)
ADT (Y vs N) MLE-Logistic		10/55, 17.8 (0.0, 36.2)	
	42/153, 27.2 (7.4, 47.0)	34/153, 22.1 (4.2, 40.1)	38/153, 25.1 (6.3, 43.9)
PSA (<2.0mg/mL vs ≥ 2.0mg/mL) Empirical	40/139, 28.8 (21.3, 36.3)	34/139, 24.5 (17.3, 31.6)	37/139, 26.6 (19.3, 34.0)
	48/63, 76.2 (65.7, 86.7)	52/63, 82.5 (73.2, 91.9)	46/63, 73.0 (62.1, 84.0)
TP/Missing PSA	1/6	1/6	1/6
PSA (<2.0mg/mL vs ≥ 2.0mg/mL) MLE-Logistic	40/139, 28.5 (8.6, 48.4)	29/139, 9/139, 20.7 (3.9, 37.5)	
	55/63, 87.0 (68.8, 100)	44/63, 69.9 (42.2, 97.6)	

Source: FDA statistical reviewer analysis

Abbreviations: CDR = correct detection rate, TP = true positive, FP = false positive, MLE = maximum likelihood estimates, RT = radiotherapy, ADT = androgen deprivation therapy, PSA = prostate-specific antigen

[1]Empirical estimate

[2]MLE using logistic regression model with covariates of [age (<65 vs ≥ 65 years), prior treatment (surgery, RT, ADT), PSA (<2.0 mg/mL vs ≥ 2.0 mg/mL)] in which the number of TP results is predicted by the model

Region-level PPV versus patient-level PPV

Table 55 shows the number and percentage of PET positive patients with composite reference standard data by region for each reader. Over half of patients with composite reference standard data had results in the pelvic lymph nodes (59%, 55%, and 56%). The percentage of patients with composite reference standard results at prostatic, extra-pelvic lymph node or bone regions were between 22% and 38%. Only small percentage of patients with composite reference standard data had results in the visceral/soft tissue region (7%, 9%, 6%).

Table 55. Region-level composite reference standard data for PET positive patients by reader in CONDOR

Region	Patients with composite reference standard data (% of total)		
	Reader 1	Reader 2	Reader 3
Prostatic	39 (38%)	36 (36%)	36 (36%)
Pelvic Lymph Nodes	61 (59%)	55 (55%)	55 (56%)
Extra-pelvic Lymph Nodes	26 (25%)	23 (23%)	23 (23%)
Bone	24 (23%)	22 (22%)	23 (23%)
Visceral/Soft-tissue	7 (7%)	9 (9%)	6 (6%)
Total	104	100	99

Source: FDA statistical reviewer analysis

We conducted additional exploratory analyses in evaluable patients by comparing region-level PPV with patient-level PPV by reader (Table 56) and also by baseline PSA level (Table 57), with patient-level PPV and region-level PPV calculated without accounting for correlation among regions within a patient. We note that region-level PPV results calculated accounting for correlation among regions within a patient when possible were similar to those without accounting for correlation.

Table 56 showed considerable decrease from patient-level PPV (86%, 87%, and 85%) to region-level PPV (67%, 70%, and 67%) for all three readers in the evaluable patients. Upon further investigation, it was found that this considerable decrease was due to the relatively high percentage of patients (24%, 25%, and 24%) having inconsistent region-level results in which both true positive region(s) and false positive region(s) were observed within the same patient. Since a single true positive region defined a true positive patient no matter how many false positive regions the same patient had, a relatively low region-level PPV could still result in high patient-level PPV while high region-level PPV will always result in high patient-level PPV.

Table 56. PPV results at patient-level and at region-level by reader in CONDOR

	All Patient (n=208)		
	Patient-Level PPV: point estimate (95% CI)	**Region-Level PPV[1]: point estimate (95% CI)**	**# and % of patients with both TP and FP regions**
Reader 1	89/104, 0.86 (0.79, 0.92)	105/157, 0.67 (0.60, 0.74)	25/104, 24%
Reader 2	87/100, 0.87 (0.80, 0.94)	101/145, 0.70 (0.62, 0.77)	25/100, 25%
Reader 3	84/99, 0.85 (0.78, 0.92)	96/143, 0.67 (0.59, 0.75)	24/99, 24%

Source: FDA statistical reviewer analysis

Abbreviation: PPV = positive predictive value, TP = true positive, FP = false positive

[1] Region-level PPV calculated without accounting for correlation among regions within a patient

Similar findings were observed when comparing region-level PPV with patient-level PPV by reader and baseline PSA level in the evaluable patients (Table 57).

Table 57. PPV results at patient-level and region-level by reader and baseline PSA level in CONDOR

		All Patient (n=208)		
	PSA level (ng/ml)	**Patient-level PPV: point estimate (95% CI)**	**Region-level PPV[1]: point estimate (95% CI)**	**#, percent of patients with both TP and FP regions**
Reader 1	Miss	1/2, 0.50 (0.09, 0.91)	1/4, 0.25 (3.4, 0.71)	1/2, 50%
	[0-0.5)	11/15, 0.73 (0.48, 0.90)	11/18, 0.61 (0.39, 0.84)	3/15, 20%
	[0.5,1)	12/16, 0.75 (0.50, 0.90)	12/18, 0.67 (0.45, 0.88)	1/16, 6%
	[1,2)	17/20, 0.85 (0.63, 0.96)	19/30, 0.63 (0.46, 0.81)	5/20, 25%
	[2, ∞)	48/51, 0.94 (0.83, 0.99)	62/87, 0.71 (0.62, 0.81)	15/51, 29%
Reader 2	Miss	1/1, 1.00 (0.17, 1.00)	1/3, 0.33 (5.6, 0.80)	1/1, 100%
	[0-0.5)	10/13, 0.77 (0.49, 0.93)	10/14, 0.71 (45.0, 0.89)	1/13, 8%
	[0.5,1)	10/13, 0.77 (0.49, 0.93)	10/15, 0.67 (41.5, 0.85)	2/13, 15%
	[1,2)	14/18, 0.78 (0.54, 0.92)	16/24, 0.67 (0.48, 0.86)	2/18, 11%
	[2, ∞)	52/55, 0.95 (0.85, 0.99)	64/89, 0.719 (0.626, 0.812)	19/55, 35%
Reader 3	Miss	1/2, 0.50 (0.09, 0.91)	1/4, 0.25 (3.4, 0.71)	1/2, 50%
	[0-0.5)	11/15, 0.73 (0.48, 0.90)	11/17, 0.65 (0.42, 0.87)	2/15, 13%
	[0.5,1)	11/15, 0.73 (0.48, 0.90)	11/16, 0.69 (44.1, 0.86)	1/15, 70%
	[1,2)	15/18, 0.83 (0.60, 0.95)	16/21, 0.76 (54.5, 0.90)	1/18, 6%
	[2, ∞)	46/49, 0.94 (0.83, 0.99)	57/85, 0.67 (0.57, 0.77)	19/49, 39%

Source: FDA statistical reviewer analysis

Abbreviation: PPV = positive predictive value, TP = true positive, FP = false positive

[1] Region-level PPV calculated without accounting for correlation among regions within a patient

8.4. Conclusions and Recommendations

Although there was no pre-specified imputation method for the primary efficacy endpoints of OSPREY Cohort A and CONDOR, and model-based imputation approaches may not be reliable due to potential bias in the collection of composite reference standard data, extensive exploration of various other imputation approaches supports the efficacy of piflufolastat F 18 PET. The review team further finds that the benefit of piflufolastat F 18 outweighs its risks. The Applicant has presented sufficient evidence to warrant the approval of piflufolastat F 18 for PET imaging of prostate cancer in patients with suspected metastasis who are candidates for initial definitive therapy or in whom recurrence is suspected based on elevated PSA levels.

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

Prostate cancer incidence is essentially zero in the pediatric population. Thus, it is not feasible to conduct pediatric studies for the proposed indication. On August 14, 2019, the FDA Pediatric Review Committee agreed to grant a full waiver of pediatric studies.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Section 1. INDICATIONS AND USAGE

- (b) (4)
- The indicated patient populations were defined as 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.

Section 2. DOSAGE AND ADMINISTRATION

- The radioactivity dose was defined as a range of 8 mCi to 10 mCi along with a single target value of 9 mCi to reflect variability in dosing in the confirmatory trials.
- Based on the Applicant's analysis (Table 29) of dose to scan time in PyL 3301 (CONDOR), a statement that starting image acquisition more than 90 minutes after injection may adversely impact imaging performance was added to section 2.4.
- Criteria for determining whether radiotracer uptake should be considered suspicious were edited to clarify that the background activity assessment should account for expected physiologic uptake.
- The radiation dosimetry estimates were adjusted to account for the range of recommended dose. Standard deviation values were added to the dosimetry table to convey the degree of uncertainty for the absorbed dose estimates.

Section 5. WARNINGS AND PRECAUTIONS

- Consistent with the labeling of other PET drugs approved for prostate cancer imaging, language was added regarding the non-specificity of ^{68}Ga PSMA-11 for prostate cancer. Given the context, other information in the labeling, and precedent in the labeling of other PET drugs, it was not deemed necessary to qualify this language with a statement that efficacy for detecting cancers other than prostate cancer has not been established.
- The potential for serum PSA level to affect test performance in the biochemical recurrence population was added.
- The potential for Gleason score and tumor stage to affect test performance in patients imaged prior to initial definitive therapy was added.
- A new subsection was added to describe the risk of hypersensitivity reaction.

Section 6. ADVERSE REACTIONS

- The reported case of hypersensitivity reaction was moved (b) (4) into the text.

Section 7. DRUG INTERACTIONS

- A statement was added to convey that androgen deprivation therapy as well as other therapies targeting the androgen pathway, such as androgen receptor antagonists, might affect the uptake of ^{68}Ga PSMA-11 in prostate cancer. It was also stated that the effect of these treatments on test performance has not been established.

Section 10. OVERDOSAGE

- Based on general radiation protection principles, instructions to encourage hydration and frequent voiding, consider use of a diuretic, and estimate the patient radiation effective dose in the case of overdose were added.

Section 14. CLINICAL STUDIES

- Additional detail was provided for the study design and results of the PyL 2301 (OSPREY) Cohort A and PyL 3301 (CONDOR) studies.
- (b) (4) The numerical estimates of test performance provided by the adequate and well-controlled trials were considered more reliable and were included in the labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

A risk evaluation and mitigation strategy is not needed for piflufolastat F 18.

13 Postmarketing Requirements and Commitment

No postmarketing requirement or commitment is required for this application.

14 Division Director (Clinical) Comments

I concur with the reviewers' assessments and their recommendation for approval of the application.

15 Office Director (or designated signatory authority) Comments

I concur with the Division's assessment and the recommendation for approval.

16 Appendices

16.1. References

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16.2. Financial Disclosure

The integrity of the efficacy studies was not affected by financial considerations.

Covered Clinical Study (Name and/or Number): PyL 2301 (OSPREY)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 172		
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): 4		
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: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: 1		
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): PyL 3301 (CONDOR)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 223		
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): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
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)

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