Phase 2 Study of ^{18}F-DCFPyL Positron Emission Tomography (PET) in Men with Intermediate or High Risk Biochemically Recurrent Prostate Cancer

INSTITUTION: UPMC Hillman Cancer Center

PROTOCOL NUMBER: HCC 20-009

STUDY PHASE: Phase 2

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INVESTIGATIONAL PRODUCT: ^{18}F-DCFPyL

Provided by Progenies Pharmaceuticals, Inc.
c/o Lantheus Medical Imaging, Inc.
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Good Clinical Practices

This clinical investigation will be performed in compliance with the protocol, the Declaration of Helsinki, Good Clinical Practices as set forth in the ICH Guidelines for Good Clinical Practice, and applicable local regulatory requirements.

Confidentiality Statement

This document contains confidential information of the Sponsor. This information is to be disclosed only to the recipient study staff and the Institutional Review Board or Institutional Ethics Committee reviewing this protocol. This information can be used for no other purpose than evaluation or conduct of this study without prior written consent from the Sponsor.

PRINCIPAL INVESTIGATOR SIGNATURE

Title:	Phase 2 Study of ^{18}F-DCFPyL Positron Emission Tomography (PET) in Men with Intermediate or High Risk Biochemically Recurrent Prostate Cancer
Protocol Number:	HCC 20-009

My signature below confirms that I have read and approved this protocol and assures that this clinical study will be conducted according to all requirements of this protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines.

Electronically signed by: Asfiok Mulhukrishnan Reason: I approve this agreement Date: Oct 21. 2021 13:05 EDT

[Signature of Principal Investigator]

Ashok Muthukrishnan, MD

[Principal Investigator Printed Name]

Oct 27, 2021

Date

SYNOPSIS

Name of Sponsor	Ashok Muthukrishnan, MD
Investigational Product	^{18}F-DCFPyL
Indication (phase)	Phase 2
Title of Study	Phase 2 Study of ^{18}F-DCFPyL Positron Emission Tomography (PET) in Men with Intermediate or High Risk Biochemically Recurrent Prostate Cancer
Protocol Date	10/21/2021

STUDY LOCATIONS

UPMC Hillman Cancer Center
UPMC Magee-Women's Hospital
UPMC Shadyside Hospital

OBJECTIVES

Primary Objective:

To determine the positive predictive value (PPV) of ^{18}F-DCFPyL Positron Emission Tomography (PET) on a per-patient basis in men diagnosed with prostate cancer with increasing PSA levels.

Secondary Objective:

To determine the PPV of ^{18}F-DCFPyL PET on a per-region basis, specifically focusing on the prostate or prostate bed, pelvis, extra pelvis, and bones.

ENDPOINTS

Primary Endpoint:

Positive predictive value (PPV) of ^{18}F-DCFPyL PET (per-patient): Number of true positives (TP) divided by number of TP plus number of false positives (FP) as detailed in Section 3.5.1.

Secondary Endpoint:

Positive predictive value (PPV) of ^{18}F-DCFPyL PET (per-region): TP/TP + FP as detailed in Section 3.5.1.

Name of Sponsor	Ashok Muthukrishnan, MD
Investigational Product	^{18}F-DCFPyL
METHODOLOGY	
Study Design	This is an interventional, single group assignment, prospective non-randomized, open label Phase 2 trial designed to evaluate the PPV of ^{18}F-DCFPyL PET imaging in men diagnosed with prostate cancer with increasing prostate-specific antigen (PSA) levels. Eligible patients will undergo baseline assessments as per the Schedule of Study Activities in Appendix A. A schematic of the study design can be found in Appendix B. Approximately 300 participants are planned for enrollment in this study. Participants will receive a single dose of ^{18}F-DCFPyL and undergo a PET imaging study. The PET imaging maybe repeated at a later date if the biopsy of the lesion is negative and if the lesion is present on follow-up imaging.
Intervention	The intervention is a PET CT scan with a single dose of the radiolabeled prostate-specific membrane antigen (PSMA) ligand, ^{18}F-DCFPyL. ^{18}F-DCFPyL PET will be acquired using a GE Discovery PET-CT scanner.
Intervention Duration	Patients meeting study eligibility criteria will receive one dose of ^{18}F-DCFPyL supplied by the current Good Manufacturing Practice (cGMP)-compliant PET production facility and will be monitored for safety for 120 minutes following administration.
Investigational Agent and Formulation	^{18}F-DCFPyL Injection is an ^{18}F-labeled small molecule that targets the extracellular domain of PSMA. It is a sterile, clear particle-free solution supplied at a specific activity of at least 1000 mCi/μmol at the Time of Administration (TOA), and a radioactivity concentration (RAC) of 1-90 mCi/mL at the Time of Calibration (TOC).
Dose and Route of Administration	One intravenous catheter will be placed for radiopharmaceutical administration. Patients will be injected with :'S 333 MBq (:'S *9* mCi) of ^{18}F-DCFPyL via this catheter. The dose range for ^{18}F-DCFPyL will be 7 - *9* mCi.

Name of Sponsor	Ashok Muthukrishnan, MD
Investigational Product	^{18}F-DCFPyL
SUBJECT POPULATION	
Number of Patients Planned for Enrollment	Approximately 300 participants are planned for enrollment in this study.
Inclusion Criteria	Patients must meet all inclusion criteria to be considered eligible for participation in the study. Male patients 2: 18 years of age. To be eligible to participate in this trial, subjects must meet all of the following criteria: • Histologically confirmed diagnosis of prostate cancer • Biochemical recurrence was defined as a PSA of 0.2 or more ng/mL measured more than 6 weeks after prostatectomy or a PSA of2 or more ng/mL rise above nadir fo11owing radiation therapy (ASTRO Phoenix consensus definition) • If PSA values are reported in double decimal points, it will be rounded to the nearest single value decimal point (e.g., 0.14 will be rounded to 0.1 and 0.15 - 0.19 will be rounded to 0.2) • Age 2: 18 years of age • Eastern Cooperative Oncology Group (ECOG) performance status :S 2 (Karnofsky 2: 60%) • Ability to understand and willingness to sign a written informed consent document • Willing to comply with clinical trial instructions and requirements

Name of Sponsor	Ashok Muthukrishnan, MD
Investigational Product	^{18}F-DCFPyL
Exclusion Criteria	Patients meeting any of the exclusion criteria **will not be eligible** for participation in the study. • History of another active malignancy within 3 years, other than basal cell and squamous cell carcinoma of the skin • Presence of prostate brachytherapy implants unless approved by the PI • Administration of another radioisotope within five physical half-lives of trial enrollment • Radiation or chemotherapy within 2 weeks prior to trial enrollment • Estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m2 • Serum total bilirubin > 3 times the upper limit of normal • Aspartate transaminase (AST) or alanine aminotransferase (ALT)> 5 times the upper limit of normal • Inadequate venous access • Claustrophobia or any other condition that would preclude PET 1magmg • Patients must not be receiving ADT except per criteria directly below. Patients who received ADT in the past must have a serum testosterone that is recovered to at least 100 ng/dL. • Patients who have been on ADT +/- novel hormonal agent (NHA) and developed MO CRPC.

ASSESSMENTS

Efficacy	PET imaging evaluated qualitatively and semi-quantitatively.
Safety	Patient safety will be evaluated based on incidence and nature of adverse events (AEs) and severe AEs (SAEs) or findings on physical examination.

Name of Sponsor	Ashok Muthukrishnan, MD
Investigational Product	^{18}F-DCFPyL
STATISTICAL METHODS AND ANALYSIS	
Efficacy	PPV will be estimated by the number of true positives (TP) divided by number of patients who are tested positive (i.e., TP + FP) based on the PET imaging, with the corresponding exact 95% confidence intervals (Cis) being reported. The determination of TP and positive testing is detailed in Section 3.5.1. All patients will be followed up for histopathologic analysis, conventional imaging (CT, MRI and/or bone scan) and/or serum PSA after focal salvage therapy acquired during clinical routine. Combination of (in descending priority) histopathologic analysis, imaging, and PSA follow-up after local/focal therapy will be taken as composite reference standard. Validation will be performed by the unblinded local investigators after reviewing images and reports, following prespecified criteria of the study protocol. In patients with follow-up, positive ^{18}F-DCFPyL PET findings will be validated as true or false-positive results. Region negative on ^{18}F-DCFPyL PET, but with subsequently confirmed prostate cancer by histopathologic analysis, will be considered false-negative results. True negative will not be defined.
Safety	The safety and tolerability of ^{18}F-DCFPyL Injection will be assessed using the incidence, nature, and severity of adverse events up to **1** day following infusion. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CT	Computerized tomography
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
1B	Investigator Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous(ly)
MBq	Megabecquerel
MRI	Magnetic resonance imaging
PC	Prostate cancer
PET	Positron emission tomography
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
SAE	Serious adverse event
SRT	Salvage radiation therapy
Tmax	Time to maximum plasma concentration
t112	Half-life
WBC	White blood cell

1. BACKGROUND AND RATIONALE

1.1 INTRODUCTION

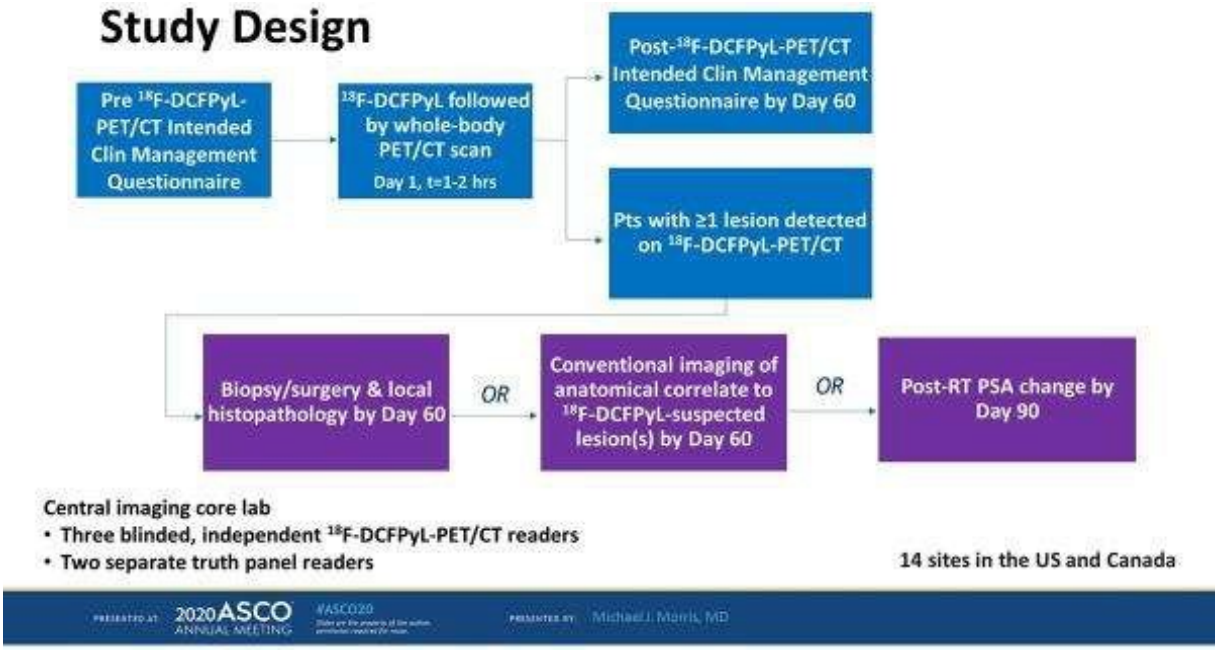
Prostate cancer is the most common cancer among men in the US with an estimated 174,650 new cases diagnosed yearly, and it is the second leading cause of cancer- related death in men [1]. Most men who die of prostate cancer succumb to metastatic, recurrent disease. Thus, imaging modalities that can detect, monitor, and restage residual, recurrent locoregional disease, and metastatic disease are highly desirable. Conventional anatomic and functional imaging including contrast-enhanced computed tomography (CT), [^{99}mTc] methylene diphosphonate (MDP) bone scan, ultrasound, or magnetic resonance imaging (MRI) may not be sufficiently sensitive and specific for detection of prostate cancer lesions [2-5].

Tumors typically exhibit abnormally high metabolism and this mechanism has been exploited for imaging cancers. Positron emission tomography (PET) using 2-deoxy-2-[1^{8}F]fluoro-D-glucose (FDG PET), the clinical standard for a number of cancers, has demonstrated diverse results in prostate cancer imaging [6-9]. Other tumor metabolism-based approaches tested in prostate and other cancers are the use of labeled choline, taking advantage of the increased expression of choline kinase (ChKa) in tumor cells [10], or increased uptake of amino acids such as methionine or leucine.^{11}C Choline was approved by the US Food and Drug Administration (FDA) in 2012 for imaging prostate cancer; however, the sensitivity of ^{11}C choline PET imaging is limited in extraprostatic lesions [11-15]. Recently, the synthetic L-leucine analog trans-l-amino-3-^{18}F-fluoro-cyclobutane carboxylic acid (1^{8}F-FACBC), or ^{18}F-fluciclovine (Axumin®), was approved by the FDA as a PET imaging agent for use in men with suspected recurrence of prostate cancer based on elevated blood prostate specific antigen (PSA) levels following prior treatment [16]. However, both ^{11}C-choline and ^{18}F-fluciclovine uptake are not specific for prostate cancer, and their imaging performance are not as reliable in patients with blood PSA levels < 2 ng/mL.

The high unmet need to accurately detect known or suspected recurrent or metastatic prostate cancer as early as possible has prompted the introduction of novel, prostate-specific membrane antigen (PSMA)-targeted PET tracers have for imaging prostate cancer with superior accuracy to facilitate appropriate disease management decisions [17-22]. Low-molecular-weight agents that bind to the PSMA, which is highly expressed in both primary and metastatic prostate cancer, have proven to be particularly effective [23-25]. A novel highly selective, low-molecular weight PSMA-targeted PET radiotracer with high specific activity, ^{18}F-DCFPyL, was discovered at Johns Hopkins University School of Medicine (JHU) and in-licensed to Progenies in 2015. Progenies has completed the clinical development of ^{18}F-DCFPyL and has recently submitted an NDA to support regulatory approval of ^{18}F-DCFPyL.

In the recent CONDOR trial, Morris et al studied 208 men with biochemically recurrent prostate cancer with a median PSA of 0.8 who underwent imaging with this tracer. The study included patients with PSA 2: 0.2 ng/mL in the post-radical prostatectomy patient and 2: 2.0 ng/mL in the post-RT or cryotherapy patient. The primary endpoint of the study was the correct localization rate (CLR), which is defined as the percentage of patients who had at least

one lesion on PET which correlated with either pathology, correlative imaging, or PSA response. Their study design in depicted in the image below:

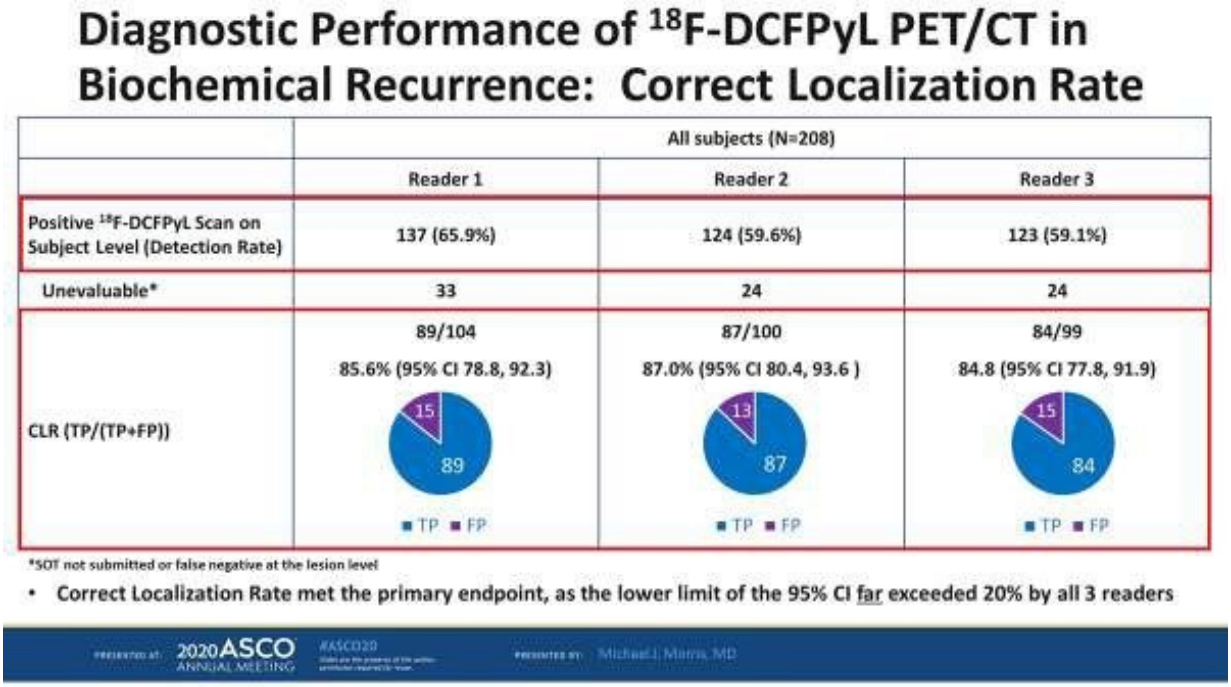


The median age was 68, with a median of 5.9 years from the time of original prostate cancer diagnosis. About half the patients had received radical prostatectomy only, 35% received RP and RT, and 15% received only RT. Most (73%) had a Gleason< 8 and 34% of patients had a PSA < 0.5. In terms of detecting disease with ^{18}F-DCFPyL-PET/CT, 59-65% of patients had positive imaging findings by PET. Of note, all of these patients had no evidence of disease with standard of care imaging. Of the positive findings, the majority of patients had clinical localization.

The CLR rate was 85 - 87% amongst the three PyL PET/CT readers. CLR was highest amongst patients with a PSA > 5 (96%) but remained high even in patients with a PSA < 0.5 (73%). For patients with a PSA > 5, PyL PET detected disease in 96% of patients and up to 36% of patients with a PSA < 0.5.

63.9% of the subjects had a change in the intended management after the PSMA PET scan, 78.6% were attributable to positive and 21.4% to negative PSMA PyL scans. 131/205 (64%) of patients had a change in intended management after PyL PET/CT. 21% of patients had a change in goal of treatment from non-curative intent to curative intent. The most common change was changing from salvage local therapy to systemic therapy (58/131). Other changes included

changing from systemic therapy to salvage therapy (43/131), changing from treatment to observation (9/131). PyL was well tolerated and the most common AE was headache (n=4, 1.9%).



The CONDOR study met its primary endpoint, demonstrating excellent diagnostic performance of DCFPyL PET/CT imaging in men with biochemically recurrent prostate cancer even at low PSA values. The CONDOR data has demonstrated DCFPyL-PET can detect disease in the majority of patients with a PSA>5 and even in a third of patients with a PSA < 0.5 More importantly, this detection leads to a change in management for the majority of patients, some even changing treatment intent from palliative to curative [60].

1.2 RATIONALE FOR DEVELOPING PROSTATE CANCER IMAGING AGENTS

Prostate cancer is a significant public health problem affecting more than 2.3 million men in the US and another 4 million in Europe. Annually, nearly 174,650 and approximately 450,000 new cases of prostate cancer are diagnosed in the US and Europe, respectively [1, 26]. It was estimated that there were 359,000 prostate cancer associated deaths worldwide in 2018 [27]. The mortality from the disease is second only to lung cancer in men **[1,** 26]. An estimated $8 billion is currently

spent annually in the US on surgery, radiation, drug therapy, and minimally invasive treatments of prostate cancer [28].

Several conventional imaging modalities are currently used for the diagnosis, staging and prognosis of prostate cancer metastases. Conventional cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) rely on anatomical changes (lesions> 1 cm), often resulting in missed lymph node metastases and has low sensitivity. Approximately one quarter of high risk prostate cancer patients have regional lymph node metastases based on postoperative histological evaluation, and half of these patients may already have bone metastases based on conventional bone scans [29, 30]. More accurate preoperative staging, better surgical planning, in combination with salvage dissection or radiation of extraprostatic lesions, may improve surgical planning and increase cure rates, especially in patients with pre- operatively diagnosed oligometastases. Similarly, in patients with recurrent or metastatic disease, early and accurate localization of recurrent or metastatic disease may afford benefits ranging from timely initiation of curative interventions, such as salvage lymph node dissection or radiation, to timely onset of systemic therapy. Nodal enlargement of metastases occurs relatively late in the progression of prostate cancer and neither CT nor MRI are effective at detecting the often microscopic lymph node metastases at the earliest stages of disease progression. Additionally, nodal enlargement can also be caused by infection or inflammation, thereby reducing the specificity.

Meta-analyses of 24 published studies reveal that CT and MRI perform equally poorly in the detection of lymph node metastases from prostate cancer [31]. Results of pooled sensitivity and specificity are 42% and 82%, respectively, for CT and 39% and 82%, respectively, for MRI. Thus, the reliance on either CT or MRI may misrepresent the patient's true status regarding nodal metastases, and misdirect the therapeutic strategies offered to the patient [31]. Radionuclide bone scans are commonly used for monitoring bone metastases. However, as bone scans detect tissue remodeling, as opposed to tumor burden, false positives can be caused by inflammation, previous bone injuries, and arthritis, especially in older men [32].

One of the most challenging aspects of clinically managing prostate cancer is the development of suspected or known disease recurrence after initial definitive therapy. Rising PSA after initial definitive therapy is known as biochemical recurrence (BCR) of prostate cancer and may occur in 20-30% of prostate cancer patients before a more definitive diagnosis of metastatic disease can be established by conventional imaging modalities [33-36].

Therefore, new agents that will detect and localize the primary tumor, as well as small metastatic lesions, with high sensitivity and specificity are essential to more accurately diagnose and stage the disease and monitor therapy.

This particular study aims to focus on the detection of metastatic disease or local recurrence early on in prostate cancer patients with biochemical recurrence. This group of prostate cancer patients after definitive local therapy currently have limited imaging options in the United States. The current standard-of-care imaging tests detect local recurrence or metastatic lesions long after when the serum PSA levels become detectable. Also, these imaging tools are not sensitive or

specific enough to detect tumor recurrence. In addition, the therapeutic options for such of group of patients are not clearly delineated in current clinical practice as the evidence of disease and its location are not easily documented by imaging early on when a definitive therapy could make a difference in patient outcomes. This DCFPyl PSMA PET imaging tool holds a great deal of promise as evidenced from multiple studies from similar PSMA molecular imaging tracers, notably the recently published data from CONDOR trial. PSMA PET imaging has also become standard-of-care elsewhere in several countries in biochemically recurrent prostate cancer patients.

The recent CONDOR trial data has shown PSMA PET imaging in extremely valuable imaging tool in most patients with a PSA > 5 and even in one-third of patients with a PSA < 0.5. Their primary endpoint was novel in that they were interested in the correct localization rate (CLR), which is defined as the percentage of patients who had at least one lesion on PET which correlated with either pathology, correlative imaging, or PSA response, which was found to be 85 - 87%. The CLR was highest in PSA > 5, but even for those with< 0.5 it was as high as 73%.

Our study intends to determine the positive predictive value of 18F-DCFPyL Positron Emission Tomography (PET) as the primary endpoint on a per-patient basis in men diagnosed with prostate cancer with increasing PSA levels, and to evaluate the PPV of 18F-DCFPyL PET on a per-region basis, specifically focusing on the prostate or prostate bed, pelvis, extra pelvis, and bones, as a secondary endpoint. This information we believe will help understand the PSMA tracer from another perspective and provide a more useful insight and serve as complementary statistics to the CONDOR trial [60].

1.3 TARGETING PSMA FOR PROSTATE CANCER DETECTION

PSMA, also known as folate hydrolase I (FOLHI) or glutamate carboxypeptidase II (GCPII), is a trans-membrane, 750-amino acid type II glycoprotein primarily expressed in normal human prostate epithelium at very low levels, if at all, but is highly upregulated in prostate cancer, including metastatic disease.

PSMA is a unique exopeptidase with reactivity toward poly-gamma-glutamated folates that is capable of sequentially removing the poly-gamma-glutamyl termini [37, 38]. Since PSMA is expressed by virtually all prostate cancers and its expression is further increased in poorly differentiated, metastatic and hormone-refractory prostate carcinomas, it is a very attractive target for developing agents for the diagnosis and staging of this disease [39-41]. In addition to high expression in malignant prostatic tissue and being directly related to tumor aggressiveness [42], lower levels of PSMA have also been detected in renal proximal tubules, cells of the intestinal brush border membrane, rare cells in the colonic crypts, the brain, salivary glands [25, 39, 43, 44], and in the neovasculature of nonprostatic solid carcinomas (e.g., renal cells, breast, colon, pancreas, melanoma, and lung carcinoma) [23]. A radiolabeled anti-PSMA monoclonal antibody (mAb) 7El l, marketed as Indium 111 ProstaScint® (capromab pendetide), is currently used to detect prostate cancer nodal metastasis and recurrence. ProstaScint was first approved for

marketing by the FDA in 1996, and while still available today, it is rarely used in practice due to a number of logistical and clinical limitations [45]. Furthermore, ProstaScint targets the intracellular domain of PSMA and is therefore thought to bind to mostly necrotic portions of the prostate tumor [40].

To overcome ProstaScint's limitations, radiolabeled monoclonal antibodies that bind to the extracellular domain of PSMA have been developed, and have been shown to accumulate in PSMA-positive prostate tumors in animals [38]. Initial promising results in man from various phase 1 and 2 trials have utilized PSMA as a therapeutic target [46, 47].

While monoclonal antibodies hold promise for tumor detection and therapy, there has been relatively limited clinical success outside of hematological cancers due to their low permeability in solid tumors and slow clearance from the circulating blood pool. Smaller molecular weight compounds with higher permeability into solid tumors are more likely to provide a distinct and definitive advantage in achieving higher percent uptake per gram of tumor tissue and a high percentage of specific binding. Small molecules are also expected to have improved blood clearance and tissue distribution in normal tissues compared with antibodies, thus enhancing the target-to-background ratio and thereby making lesion detection more conspicuous.

In the past few years, a number of investigational PSMA-targeted small molecules have been synthesized and labeled with various radioisotopes to be tested for use as imaging agents for prostate cancer:

- A single photon emission computed tomography (SPECT) agent, ^{99}mTc-MIP-l 404, has completed phase 3 testing for the detection of clinically significant prostate cancer in patients with low grade (per biopsy) disease [48, 49].
- PET imaging agents, such as ^{124}I-MIP-1095, ^{18}F-DCFCBC, ^{18}F-DCFPyL, and ^{68}Ga-HBED-CC, have also generated much interest for their potential use in detecting localized and metastatic prostate cancer.

^{68}Ga-HBED-CC (^{68}Ga-PSMA) has been broadly studied in the clinical setting at academic centers. In a retrospective analysis of patients with high-risk localized disease prior to radical prostatectomy, ^{68}Ga-PSMA PET/CT imaging showed a sensitivity of approximately 93% for intraprostatic lesions and 33% for regional lymph node metastases. Specificity and positive predictive value (PPV) for lymph nodes were 100%, 100% and 69%, respectively [50]. A retrospective evaluation of data from ^{68}Ga-PSMA PET/CT imaging in patients with biochemical recurrence of prostate cancer showed high detection rates, even in patients with low (0.2 to 0.5 ng/mL) PSA (58%) [51].

Studies have also been conducted to compare ^{68}Ga-PSMA PET/CT and ^{18}F-choline PET/CT (which targets the choline transporter, not PSMA) imaging in prostate cancer: In patients with recurrent prostate cancer scheduled to undergo salvage lymphadenectomy (thus providing histopathology as the truth standard), ^{68}Ga-PSMA PET/CT showed better performance than ^{18}F-choline PET/CT with a significantly higher negative predictive value (NPV) and accuracy for the

detection of locoregional recurrent and/or metastatic lesions prior to salvage lymphadenectomy, with sensitivity of 71% vs 87%, specificity of 87% vs. 93%, and accuracy of 83% vs 92%, respectively [52]. In patients with biochemical recurrence of prostate cancer with a negative [^{18}F]-choline PET/CT, ^{68}Ga-PSMA-PET/CT identified sites ofrecurrent disease in 43.8% of the patients with negative F-choline PET/CT scans [53].

Another study was conducted to compare the detection rates of two PSMA-targeted PET agents, ^{18}F-DCFPyL and ^{68}Ga-PSMA, side-by-side in patients with recurrent prostate cancer [54]. The results showed that ^{18}F-DCFPyL PET/CT provided high image quality and visualized small prostate lesions with excellent sensitivity, similar to ^{68}Ga-PSMA.

F-18 tracers in general offer important advantages over Ga-68 tracers, including higher production capacity from the use of a cyclotron as opposed to depending on the supply from Gallium generators, and higher image resolution due to the intrinsic physical properties of F-18 (lower positron emission energy compared to Ga-68). Thus, ^{18}F-DCFPyL PET/CT may represent a promising alternative to ^{68}Ga-PSMA PET/CT for imaging prostate cancer.

Progenies is completing the clinical development of PyL with the intention of seeking regulatory approval of PyL for the detection of prostate cancer.

1.4 NAME AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

^{18}F-DCFPyL Injection is a radiolabeled small molecule that binds to the extracellular domain of prostate-specific membrane antigen (PSMA) with high affinity. PSMA is a transmembrane glycoprotein expressed by virtually all prostate cancers, and its expression is further increased in metastatic and hormone-refractory prostate carcinomas, which makes it a useful target for developing agents for the diagnosis and staging of prostate cancer. The nonclinical studies conducted with DCFPyL and ^{18}F-DCFPyL included biochemical activity, biodistribution in xenograft mice, small animal PET imaging, and a single dose IV toxicology study in rats. Data from enzyme inhibition assay showed that DCFPyL binds competitively to PSMA expressing LNCaP cells with a Ki of I. I nM. Studies in PSMA positive tumor bearing nude mice demonstrated significant tumor uptake and retention, coupled with a rapid clearance from non-target organs to provide support for the further development of ^{18}F-DCFPyL as a radiopharmaceutical for detection and localization prostate cancer in man.

Results of a I4-day single dose rat toxicology study with DCFPyL showed a NOAEL of 0.5 mg/kg, the highest dose tested. The maximum human mass dose of DCFPyL is 4 μg; which indicates a safety margin of> 1200-fold the human equivalent dose. Several investigator-initiated clinical studies with ^{18}F-DCFPyL Injection have been conducted at JHU under IND 12I,064. Safety and efficacy data are available from two of these studies (JI 418: a first in human, phase 1/2 study in men with clinically localized high to very high-risk prostate cancer, and 11545: a phase 2 study in men with an elevated PSA > 0.2 ng/mL following radical prostatectomy with pelvic

lymphadenectomy). These data demonstrate that PET imaging with ^{18}F-DCFPyL Injection at doses averaging 9 ± 1 mCi per injection is overall feasible and safe. Biodistribution following administration of ^{18}FDCFPyL Injection and optimal imaging time point were determined and radiation dose used was within limit for diagnostic radiotracers for PET.

Physiologic accumulation of ^{18}F-DCFPyL was found to correspond to the distribution of PSMA expressing organs. Accumulation in primary tumor and metastatic lesions was very high, suggesting that ^{18}F-DCFPyL Injection can be used to detect residual tumor as well as regional or distant metastases with high sensitivity and specificity. Sensitivity and specificity with ^{18}F-DCFPyL PET/CT in patients with at least localized intermediate risk prostate cancer who have undergone RP with lymphadenectomy was comparable to published ^{68}Ga-PSMA imaging data [50].50,57 Thus, results further suggest that ^{18}FDCFPyL PET/CT demonstrates efficacy in preoperative staging of patients with high-risk prostate cancer. Safety results from all JHU studies have shown that ^{18}F-DCFPyL Injection is well tolerated, with no reported serious adverse events in any of the studies. Progenies initiated the "OSPREY" phase 2/3 study (PyL2301) under a new, separate IND to investigate the safety and efficacy of PyL imaging in patients with prostate cancer in November 2016.

PyL2301 is a multi-center, open-label study entitled, PrOspective Phase 2/3 Multi-Center Study of ^{18}F-DCFPyL PET/CT Imaging in Patients with PRostate Cancer: Examination of Diagnostic AccuracY (OSPREY; NCT02981368). The study completed in September 2018; a total of 385 subjects with prostate cancer received a dose of ^{18}F-DCFPyL Injection in PyL2301. A total of 81 treatment-emergent adverse events (TEAEs) were reported in 51 (13.2%) subjects. A total of 5 subjects (1.3%) experienced TEAE(s) that were National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 2: Grade 3 in severity; all were Grade 3 and none were more severe. Fatigue, dysgeusia, and headache were the only TEAEs that occurred in 1% or more of dosed subjects.

Seven treatment emergent serious adverse events (SAEs) were reported within the protocol-specified period. All seven SAEs were assessed as unrelated to study drug. There were no deaths or AEs that led to study discontinuation. A phase 3 study, PyL3301, entitled, "A Phase 3, Multi-center, Open-label Study to Assess the Diagnostic Performance and Clinical Impact of ^{18}F-DCFPyL PET/CT Imaging Results in Men with Suspected Recurrence of Prostate Cancer" (CONDOR; NCT03739684) was initiated in November 2018. Suspected recurrence is based on rising PSA after definitive therapy despite negative or equivocal findings for prostate cancer on standard of care baseline imaging. The study is planned to be conducted in 15 sites in the US and Canada.

1.5 RESULTS OF NONCLINICAL STUDIES

A description of the use ofDCFPyL in non-clinical studies can also be found in the Investigator's Brochure.

The nonclinical studies conducted with DCFPyL and ^{18}F-DCFPyL included biochemical activity, biodistribution in xenograft mice, small animal PET imaging, and a single dose IV toxicology study in rats. All of these studies were submitted by JHU to FDA under IND 121,064.

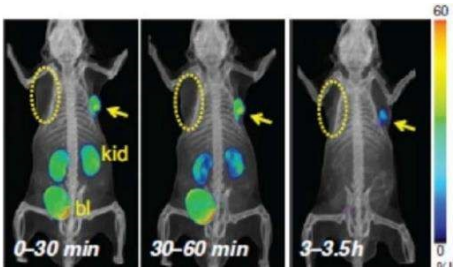
1.5.1 Summary of Pharmacology Studies

The biochemical activity ofDCFPyL was determined in an enzyme-inhibition assay using lysates of LNCaP cells in the presence of 4 µmol/L NAAG and DCFPyL (0.01-100 mmol/L) at 37°C for two hours. The amount of released glutamate was measured by incubating with a working solution of the Amplex Red glutamic acid kit at 37°C for 30 minutes. Enzyme inhibitory constants **(Ki** values) were generated using the Cheng-Prusoff conversion. DCFPyL potently inhibited PSMA's NAAGase activity with a Ki of 1.1 ± 0.1 nM.

A PET imaging study was conducted in a single NOD-SCID mouse implanted with PSMA-positive PC3 PIP and PSMA-negative PC3 flu xenografts. The animal was anesthetized and placed in the prone position on the gantry of a small animal PET scanner and injected intravenously with 0.38 mCi ^{18}F-DCFPyL in 200 mL of PBS. The images were then acquired as a sequence of successive whole-body images in 2 bed positions.

As shown in Figure 1, PSMA-positive PC3 PIP (arrow) and PSMA-negative PC3 flu (dotted oval) tumors were present in subcutaneous tissues posterior to opposite forearms, as indicated (kid = kidneys, bl= bladder). Intense radiochemical uptake was seen only in the kidneys and PSMA-positive PC3 PIP tumor, while no uptake was noted in PSMA-negative PC3 flu tumors. The renal uptake was partly due to specific binding of the radiotracer to proximal renal tubules and partly to excretion of this hydrophilic compound. By 3.5 h after injection, only the PSMA-positive tumor was visible with no radiochemical background in liver gastrointestinal tract.

Figure 1: Time Course of Radiochemical Uptake Following ^{18}FDCFPyL Injection in Xenograft Mouse



kid= kidneys, bl= urinary bladder [55].

1.5.2 Summary of Pharmacokinetics Studies

PSMA-positive PC3 PIP and PSMA-negative PC3 flu xenograft-bearing SCID mice were injected via the tail vein with 100 mCi of ^{18}F-DCFPyL. Mice (4 per group) were sacrificed at 30, 60, 120,

and 240 minutes post injection, organ and tissues were harvested, weighed and the tissue radioactivity was measured with an automated y-counter. The ¾ID/g was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for decay. The resulting ¾ID/g values are listed in Table 2. ^{18}F-DCFPyL showed clear PSMA-dependent uptake within a PSMA-positive PC3 PIP xenograft mouse model, reaching a value of 46.7 ± 5.8%ID/g at 30 minutes post injection, which decreased by only about 10% over the ensuing 4 hours. At 60 minutes post injection the kidney, liver, and spleen displayed the highest uptake.

Rapid clearance from the kidneys was shown, decreasing from 74.1 ± 6.6%ID/g at 30 minutes to 7.4 ± 0.9%ID/g at 4 hours. The relatively high values noted in the kidney are partially due to previously reported high expression of PSMA within proximal renal tubules. The ratio of uptake within PSMA-positive to PSMA-negative tumors ranged from 40:**1** to more than 1000: **1** over the four-hour time period of the study. A possible explanation for the increased tumor uptake of ^{18}F-DCFPyL over time could be due to ligand-mediated PSMA internalization within tumor cells. Less retention in kidney relative to tumor over time could be due to a lower degree of internalization in this tissue. Relatively low bone uptake of radioactivity(< 1% ID/g at all time points) suggests little metabolic de-fluorination of ^{18}F-DCFPyL in mice.

Table 2: Biodistribution of ^{18}F-DCFPyL in Tumor-bearing Mice (mean± SD %1D/g [n = 4])

!Organ	O min	60 min	It20 min	1240 min
Blood	1.53 ± 0.19	0.24 ± 0.05	0.43 ± 0.37	0.03 ± 0.01
Heart	0.68 ± 0.07	0.20 ± 0.11	0.06 ± 0.01	0.02 ± 0.00
Lung	1.91±0.47	0.55±0.17	0.18 ± 0.02	0.06 ± 0.00
Liver	3.88 ± 0.74	2.87 ± 0.92	2.14 ± 0.11	1.80 ± 0.39
Stomach	1.50± 1.12	0.35 ± 0.34	0.08 ± 0.03	0.02 ± 0.00
Pancreas	1.02 ± 0.53	0.26 ± 0.13	0.08 ± 0.00	0.03 ± 0.01
Spleen	7.59 ± 3.56	2.70 ± 1.28	0.69 ± 0.11	0.23 ± 0.09
Kidney	74.1 ± 6.6	42.3 ± 19.0	15.7 ± 3.3	7.42 ± 0.89
Muscle	0.39 ± 0.05	0.67 ± 0.92	0.04 ± 0.00	0.05 ± 0.05
Bone	0.82±0.16	0.42 ± 0.15	0.33 ± 0.08	0.43 ± 0.06
Sm. Intest.	0.79 ± 0.11	0.31 ± 0.12	0.11 ± 0.07	0.05 ± 0.01
Lrg. Intest.	0.73 ± 0.04	0.40 ± 0.17	0.12 ± 0.05	0.06 ± 0.01
Bladder (empty)	18.6± 18.1	9.88 ± 4.92	6.44 ± 4.42	1.54 ± 1.79
PSMA+PIP	46.7 ± 5.8	44.2 ± 9.7	39.4 ± 5.4	36.6 ± 4.3
PSMA-flu	11.17 ± 0.41	0.36 ± 0.14	0.11 ± 0.02	0.03 ± 0.01

1.5.3 Determination of Radiation Dose Estimates in Humans

Prior to first in-human exposure, the human dosimetry values were obtained using the mouse biodistribution data (Table 2 above). The mouse organ activity concentrations in %ID/g were converted to the human %ID/organ by setting the ratio of organ %ID/g to whole-body %ID/gin the mouse equal to that in humans and then solving for the human %ID/organ; the adult male phantom organ masses listed in the OLINDA/EXM 1.0 were used for the conversion. The time-activity curves were fitted using a monoexponential function. Table 3 below lists target human organ absorbed doses. The organ with the highest mean absorbed dose per unit administered activity was the urinary bladder wall, 0.15 mGy/MBq, followed by the kidneys at 0.05 mGy/MBq. Based on the dosimetry results, 9 mCi (331 MBq) could be administered without exceeding the 50 mGy critical organ dose limit (urinary bladder wall in this case), as specified in CFR 21, part 361 for a single administration of radioactive material for research use.

Table 3: Estimated Human Organ Absorbed Dose

Target organ	Absorbed dose (mGy/MBq)
Adrenals	6.46 E-03
Brain	.84 E-03
Breasts	3.97 E-03
Gallbladder wall	6.48 E-03
Lower large intestine wall	9.40 E-03
Small intestine	7.53 E-03
Stomach wall	5.27 E-03
Upper large intestine wall	6.67 E-03
Heart wall	3.26 E-03
Kidneys	.81 E-02
Liver	7.38 E-03
Lungs	3.01 E-03
Muscle	3.95 E-03
Ovaries	9.06 E-03
Pancreas	.38 E-03
Red marrow	5.35 E-03
Osteogenic cells	7.59 E-03
Skin	3.84 E-03
Spleen	6.57 E-03
Testes	7.06 E-03

Thymus	.43 E-03
Thyroid	.45 E-03
Urinary bladder wall	1.51 E-01
Uterus	1.45 E-02
Total body	**5.71 E-03**
Effective dose equivalent (mSv/MBq)	**1.80 E-02**
Effective dose (mSv/MBq)	**1.36 E-02**

1.5.4 Toxicology

1.5.4.1 Single-dose Toxicity Studies

A 14-day study was conducted to determine toxicity of DCFPyL from a single intravenous (IV) dose in Sprague Dawley Rats. The purpose of this OLP-compliant study was to evaluate the toxicity of DCFPyL on days 3 and 15 following a single intravenous dose in rats. Male and female Sprague Dawley rats were assigned to six groups (N=5/gender/group) and dosed intravenously on day 1 with 0.1 or 0.5 mg/kg DCFPyL or the vehicle control. Assessment of toxicity was based on mortality, clinical signs, body weight, body weight changes, and clinical and anatomic pathology. All rats generally gained weight and no test article-related alterations in body weight or body weight change were noted during the study. AU rats survived to the scheduled termination and remained bright, alert and responsive during the course of this study.

For clinical chemistry, hematology and coagulation samples, there were no treatment-related differences noted and there were no statistical differences between the groups at Study Day 3 or 15. No statistically significant or treatment-related differences were noted in organ weight data at Study Day 3 or 15. Microscopic findings in the Study Day 3 and Day 15 rats were considered incidental and not directly related to the test article. The test article, DCFPyL, at 0.5 mg/kg had no adverse effects in any of the tissues examined.

In conclusion, under the conditions of this study, there were no treatment related findings in Sprague Dawley rats three or fifteen days after a single intravenous dose ofDCFPyL at 0.1 mg/kg and 0.5 mg/kg. The maximum human mass dose of DCFPyL is 4 micrograms. Using the appropriate scaling factor for conversion of rat doses to human equivalent doses (HED) based on body surface area (x 0.16), the safety margins in humans is> 1200-fold HED.

1.6 RESULTS OF CLINICAL STUDIES

A description of the use of ^{18}F-DCFPyL in clinical studies can also be found in the Investigator's Brochure.

1.6.1 Previous Human Experience

Several investigator-initiated clinical studies with ^{18}F-DCFPyL Injection in prostate cancer, as well as non-prostate cancer, have been conducted at JHU under IND 121,064. Two of the studies in prostate cancer (11418 and 11545) are completed and have been published. Progenies initiated the "OSPREY" (PyL2301) study under a new, separate IND to investigate the safety and efficacy of PyL imaging in patients with prostate cancer in November 2016. The study completed in September 2018.

These studies are summarized in Table 4 below.

Table 4: ^{18}F-DCFPyL Studies: Progenies Sponsored and Published Studies from Johns Hopkins University (JHU)

Study	Title	Patient Population	# Patients Dosed
11418	Study of ^{18}F-DCFPyL, a Second Generation Low-molecular Weight PSMA-based PET radiotracer, m Patients with Advanced Prostate Cancer	Metastatic PCa Localized PCa	N=l0 N=28
11545	Pilot study of ^{18}F-DCFPyL in the Evaluation of Men with an Elevated PSA Following Radical Prostatectomy	Recurrent PCa and PSA Persistence	N=50
PyL2301 (OSPRE)	A Prospective Phase 2/3 Multi- center study of ^{18}F-DCFPyL PET/CT imaging in Patients with Prostate Cancer: Examination of Diagnostic Accuracy (OSPREY)	At least high-risk PCa (Cohort A); recurrent or metastatic PCa (Cohort B)	N=385 (268 Cohort A; 117 Cohort B)

Safety and efficacy data from these studies (11418, 11545, and OSPREY) are discussed below.

1.6.1.1 Study J1418: Study ^{18}F-DCFPyL a Second Generation Low-molecular Weight PSMA based PET Radiotracer, in Patients with Prostate Cancer

This was a first-in-human, open-label, single-arm, single-site phase 1/2 study.

The first part of this study (Phase 1) was designed to evaluate the radiation dosimetry, biodistribution, metabolism, and safety of9 mCi (331 MBq) ^{18}F-DCFPyL Injection with PET/CT **imaging in 10 men with clinically progressive metastatic prostate cancer post local therapy**

(prostatectomy, external beam radiation therapy, or brachytherapy of the prostate). To assess pharmacokinetics, metabolism, and excretion of ^{18}F-DCFPyL Injection, blood samples were obtained from the vein contralateral to the site of injection for evaluation at three time points: after 20 minutes post-injection, after 90 minutes post-injection, and at the completion of PET scanning (150 minutes post-injection). Urinary excretion was calculated at approximately 110 and 160 min post-injection.

Once preliminary safety and tolerability were established, the second, currently ongoing, phase 2 part of the study commenced. The objective of phase 2 is to evaluate the utility of ^{18}F-DCFPyL PET/CT imaging to detect areas oflocal, nodal and/or distant prostate cancer in up to 25 men with clinically-localized high to very-high risk prostate cancer as defined by the National Comprehensive Cancer Network (NCCN) (clinical T stage 2: T3a, Gleason sum 2: 8, PSA > 20 ng/mL) (NCCN high-to-very-high-risk: clinical stage 2: T2/3 or Gleason sum 2: 7 or PSA 2: 10 ng/mL) who are scheduled to undergo radical prostatectomy with pelvic lymphadenectomy.

Histopathology will be compared to ^{18}F-DCFPyL imaging for analysis of diagnostic accuracy. A single IV bolus injection of 9 mCi (333 MBq) or less of ^{18}F-DCFPyL Injection was administered to all enrolled subjects. Results for the phase 1 portion of the study are summarized below for 9 of the 10 patients imaged for whom dosimetry data are available.

No SAEs were reported. There were three adverse events reported in two subjects, all of which were considered not related to study drug. One subject reported two Grade 1 adverse events (CTCAE v4.0) of headache and epistaxis. Another subject experienced Grade 1 thrombocytopenia upon clinical lab safety assessment during the post-imaging follow-up visit, which was attributed to the start of prostate cancer therapy.

The time course of blood radioactivity is presented in Table 5 for seven evaluable subjects and demonstrates a rapid decline oflevels to approximately 50% of the initial exposure by 150 minutes.

Table 5: Blood Radioactivity Concentrations (nCi/mL) in Study J1418, Phase 1

Time point (min)	Patient Number							Mean	SD
	3	4	5	6	7	8	9		
120	33.13	5.02	12.08	23.19	27.14	28.73	26.54	**22.26**	**110.03**
190	22.28	2.65	10.21	16.95	16.68	18.10	17.71	**14.94**	**16.48**
1150	16.31	2.21	5.69	13.88	12.64	13.94	14.70	**11.34**	**5.26**

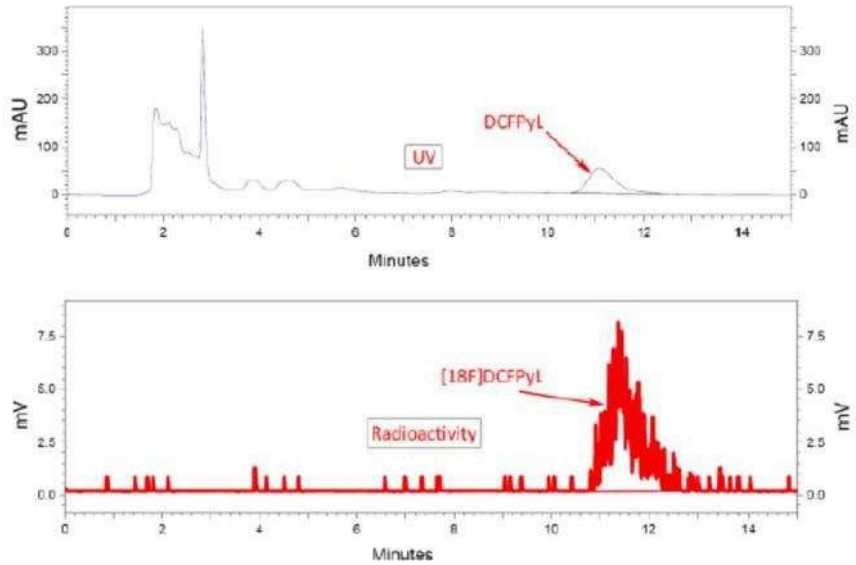
The urinary excretion expressed as % injected dose per subject is listed in Table 6 below:

Table 6: Urinary Excretion(% Injected Dose per Subject) in Study J1418, Phase 1

Time point (min)	Patient Number							Mean	SD
	3	4	5	6	7	8	9		
0-110	5.86	1.62	5.70	10.63	16.54	25.26	14.09	111.39	**8.01**
110-160	3.72	0.87	1.36	5.12	5.49	9.56	6.14	**.61**	**2.98**
0-160	9.58	2.50	7.06	15.75	22.03	34.82	20.22	115.99	**10.89**

The metabolic profiles in plasma were determined in three patients at 20, 90 and 150 minutes post-injection. Analysis of plasma samples by high-performance liquid chromatography (HPLC) up to 173 minutes post-injection demonstrated that all plasma activities were in the form of non-metabolized parent compound (Example provided in Figure 2).

Figure 2: HPLC Curves of Plasma ^{18}F-DCFPyL (Radioactivity) in One Subject at 173 min Post-injection Compared with the "Cold" Reference Standard DCFPyL (UV)



In summary, following intravenous administration, a rapid washout of ^{18}F-DCFPyL-associated activity from the blood pool and significant renal excretion with radiotracer accumulation in the bladder were observed. The only radioactive component detected in plasma samples was unchanged ^{18}F-DCFPyL. Based on PET imaging, the radioactivity detected in the small intestine was associated solely with the intestinal wall, suggesting a lack of fecal excretion.

Physiologic accumulation and excretion of ^{18}F-DCFPyL Injection was measured using serial PET/CT image data from nine patients and subsequently used to derive dosimetry calculations. Physiologic accumulation of ^{18}F-DCFPyL Injection corresponded to the distribution of PSMA-expressing organs and excretion. Outside of the tumor, the longest residence time in normal organs was observed in kidneys, liver, muscle and bladder (Table 7).

Table 7: Mean Tissue/Organ Residence Times of ^{18}F-DCFPyL in Nine Patients (Study J1418)

Organ/Tissue	Res. Time (Bq-h)/Bq
Adrenals	2.55E-04
Brain	5.26E-03
Gallbladder Wall	9.36E-04
Lower large intestine wall	3.48E-03
Stomach Wall	1.03E-02
Upper large intestine wall	2.52E-02
Heart Wall	4.32E-03
Kidneys	2.06E-01
Liver	2.59E-01
Lungs	3.92E-02
Muscle	2.88E-01
Pancreas	2.90E-03
Red Marrow	5.10E-02
Spleen	1.95E-02
Testes	1.30E-03
Thyroid	2.24E-04
Lens	2.24E-04
Lacrimal Glands	2.60E-04
Parotid Glands	1.94E-02
Submandibular Glands	6.63E-03
Total Body	1.91E+00
Remainder of Body	9.61E-01
Heart content	2.12E-02

The radiation absorbed doses (Table 8) to radiosensitive organs such as red marrow and gonads were low (0.01 mGy/MBq or less). Highest radiation exposure was observed in kidneys (0.0896 mGy/MBq), followed by the urinary bladder wall (0.0873 mGy/MBq), parotid glands (0.0495 mGy/MBq), and liver (0.0420 mGy/MBq). PSMA-expressing tissues, including the lacrimal, salivary and parotid glands, exhibited moderate radiation absorbed doses (between 0.042 mGy/MBq and 0.027 mGy/MBq). The effective dose from ^{18}F-DCFPyL was calculated to be 0.0169 mSv/MBq or 5.5 mGy (0.55 rem) for an injected dose of 9 mCi (333 MBq), which is less than other commonly used tracers for oncologic imaging such as ^{18}F-FDG.

Table 8: Mean Absorbed Dose of ^{18}F-DCFPyL in Nine Patients (Study JI418)

Organ	Mean Absorbed Dose (mGy/MBq)	SD
Adrenals	3.1 7E-02	8.04E-03
Brain	2.33E-03	4.58E-04
Breasts	4.87E-03	l.05E-03
Gallbladder Wall	1.46E-02	2.19E-03
LLIWall	1.07E-02	2.23E-03
Small Intestine	9.43E-03	1.82E-03
Stomach Wall	1.30E-02	6.75E-03
ULI Wall	1.77E-02	5.40E-03
Heart Wall	1.47E-02	2.98E-03
Kidneys	8.96E-02	3.09E-02
Liver	4.20E-02	1.02E-02
Lungs	1.13E-02	2.47E-03
Muscle	6.52E-03	9.18E-04
Ovaries	9.26E-03	1.77E-03
Pancreas	2.65E-02	9.31E-03
Red Marrow	9.94E-03	1.68E-03
Osteogenic Cells	9.70E-03	1.83E-03
Skin	4.27E-03	9.24E-04
Spleen	2.15E-02	3.85E-03
Testes	9.25E-03	2.39E-03
Thymus	5.97E-03	l.23E-03
Thyroid	1.00E-02	2.51E-03
Urinary Bladder Wall	8.73E-02	3.20E-02
Uterus	1.19E-02	2.44E-03
Lens	1.16E-03	3.23E-04
Lacrimal Glands	2.74E-02	1.45E-02
Parotid Glands	4.95E-02	2.90E-02
Submandibular Glands	4.18E-02	2.99E-02
Total Body	7.65E-03	1.13E-03
Effective Dose (mSv/MBq)	1.69E-02	l.82E-03

Quantitative uptake of ^{18}F-DCFPyL in abnormal foci, demonstrating the greatest uptake in terms of maximum standardized uptake value (SUVmax), were measured across all available PET/CT time points and used to determine the optimal imaging time point following injection. Two experienced nuclear medicine readers identified sites of abnormal uptake in a consensus read.

Most lesions were visually evident at the earliest time points and uptake was observed to increase with time while blood pool activity decreased. At approximately 1 and 2 hours, respectively, the highest uptake and lowest background activity were observed suggesting that PET/CT imaging of ^{18}F-DCFPyL as early as one hour post-injection will allow for the full extent of lesions to be evaluated in most patients.

In summary, the results from the Phase 1 portion of the study showed that PET imaging with ^{18}F-DCFPyL in patients with prostate cancer is feasible and safe at a radiation dose that is within acceptable limits for diagnostic PET radiotracers [56].

In the Phase 2 portion of the Jl418 study, the diagnostic performance of ^{18}F-DCFPyL Injection PET/CT imaging to detect areas oflocal, nodal and/or distant prostate cancer spread was assessed in 25 patients with clinically localized intermediate or higher risk prostate cancer (clinical stage 2: T2b or GS 2: 7 or PSA 2: 10 ng/mL) prior to undergoing radical prostatectomy with pelvic lymph node dissection (PLND). Areas of intra- and extraprostatic tumor spread identified with ^{l8}F-DCFPyL Injection were compared with postop histopathology as the truth standard.

All 25 subjects included in the analysis had at least high-risk PCa based on pre-surgery clinical, laboratory assessments and biopsy-based histology. ^{18}F-DCFPyL PET/CT imaging was done 1-7 days before surgery. The analysis was performed at the subject level as well as at the individual right, left side lymph node packet levels (n = 50). Eighteen (72%) subjects had Gleason score 4 + 5 = 9 or 5 + 4 = 9, and 13 (52%) subjects were pT3a and 7 (28%) were pT3b based on whole gland histopathology, and seven (28%) subjects were found to have harbored one or more PCa- positive lymph nodes. A median of 13 (range 4-45) lymph nodes was removed at the time of surgery. Notably, two subjects had bilateral lymph node involvement, resulting in a total of 9 positive lymph packets for the entire study cohort. Positive lymph nodes were typically small, with a median diameter of 3 mm (range 1-12).

Following independent image reads and adjudications, 7 (28%) subjects were confirmed to have 2: 1 site of focal radiotracer within the pelvis consistent with N1 disease. This resulted in a sensitivity and specificity of 71.4% (95% CI 29.0-96.3) and 88.9% (65.3-98.6), respectively, for the presence or absence of metastatic prostate cancer. Similar results were found in the packet-level analysis with a sensitivity of 66.7% (29.9-92.5) and a specificity of 92.7% (80.1-98.5), in good agreement with published ^{68}Ga PSMA imaging data [50]. Additionally, the readers determined that 3 (12%) subjects had PET/CT findings consistent with Mla disease (none had Mlb or Mlc). All 3 of these patients had a detectable PSA level within 6 months of surgery.

In summary, results from the phase 2 portion of the study suggest that ^{18}F-DCFPyL PET/CT may improve preoperative staging in patients with high risk prostate cancer [57].

1.6.1.2 Study J1545: Pilot Study of ^{18}F-DCFPyL PET/CT in the Evaluation of Men with an Elevated PSA Following Radical Prostatectomy

This was an open-label, single-arm, single-site phase 2 study in up to 50 subjects with an elevated PSA (2: 0.2 ng/mL) following radical prostatectomy. This study broadly includes men with PSA

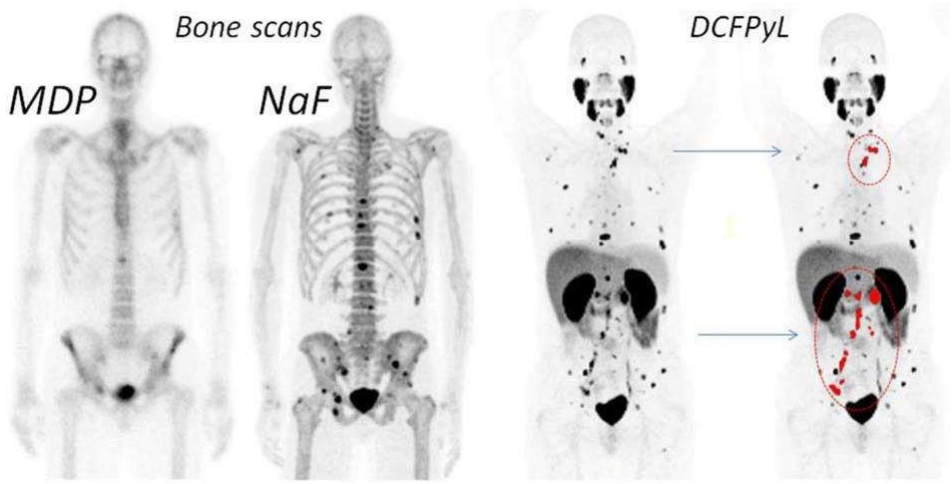
persistence and recurrent prostate cancer after surgery and aims to: 1) evaluate the safety of ^{18}F-DCFPyL Injection; 2) describe the number and location of putative sites of metastatic disease as determined by ^{18}F-DCFPyL PET/CT; and 3) correlate findings on ^{18}F-DCFPyL PET/CT with conventional imaging (bone scan and cross-sectional imaging).

Treatment response by ^{18}F-DCFPyL PET/CT following six months of standard of care therapy was also explored in select patients. A single intravenous bolus injection of 9 mCi (333 MBq) or less of ^{18}F-DCFPyL was administered. Approximately 1-2 hours after the administration of ^{18}F-DCFPyL, patients voided and whole-body CT and PET scans were acquired from the mid-thigh to the vertex of the skull. Recruitment for this study has ended, but the patients remain in follow-up and final analysis of the data has not been completed. No SAEs were reported.

1.6.1.3 Case Report from Study J1545 - Detecting Metastatic Lesions Compared to Bone Scan

Rowe et al. [58] published the case of a 45-year-old patient who had first presented approximately two years before the time of PET imaging with an elevated PSA level of 39 ng/mL and suspected clinically localized prostate cancer (biopsy GS 5+4). After radical prostatectomy and pelvic lymph node resection, his PSA remained high (10.5 ng/mL), and he received treatment with leuprolide and docetaxel, resulting in a PSA of 1.0 ng/mL. The patient was then enrolled into a series of clinical trials and received, in succession, sipuleucel-T, anti-PD-LI therapy, and enzalutamide, with persistent PSA elevations as high as 15.6 ng/mL but decreased to 1.0 ng/mL while receiving enzalutamide. At this point in his treatment course, the patient was imaged with ^{99}mTc-MDP bone scan, Na ^{18}F PET/CT, and ^{18}F-DCFPyL PET/CT. All three imaging modalities revealed extensive skeletal metastases, with the highest number of bone lesions detected with ^{18}F-DCFPyL PET/CT imaging. In addition to bone metastasis, ^{18}F-DCFPyL PET/CT also revealed numerous soft tissue lesions (Figure 3).

Figure 3: Anterior Projection Whole-body Planar ^{99}mTc-MDP Bone Scan, Anterior View of Maximum Intensity Projection (MIP) Using Na ^{18}F PET and ^{18}F-DCFPyL PET with Abnormal Lymph Node Uptake Masked in Red



1.6.1.4 PyL2301: A Prospective Phase 2/3 Multi-center study of ^{18}F-DCFPyL PET/CT imaging in Patients with Prostate Cancer: Examination of Diagnostic Accuracy (OSPREY)

PyL2301 was an open-label, non-randomized, phase 2/3, multicenter study designed to evaluate the safety and diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to determine the presence or absence of metastatic prostate cancer in subjects with at least high-risk prostate cancer who are planned for radical prostatectomy [RP] with pelvic lymph node dissection [PLND], cohort A), and subjects with radiologic evidence of local recurrence or new or progressive metastatic disease (cohort B). ^{18}F-DCFPyL PET/CT scans were centrally reviewed by three, independent readers blinded to all clinical and other imaging information. ^{18}F-DCFPyL PET/CT results were compared to histopathology (from surgery or biopsy) as the reference standard. This study was conducted in 10 sites in the United States and Canada. The study was completed in September 2018.

1.6.1.5 Efficacy Results

Three central, blinded, and independent readers evaluated the ^{18}F-DCFPyL PET/CT scans and histopathology served as the reference standard to which imaging findings were compared. In patients with at least high-risk PCa planned for RP+PLND (Cohort A), the sensitivity of ^{18}F-DCFPyL PET/CT ranged among the three central readers from 30.6-41.9% (lower bound of 95% CI: 19.2-29.7%), with specificities ranging from 96.3-98.9% (lower bound of 95% CI: 93.6-

96.0%). Additionally, the PPV and NPV ranged from 78.1-90.5% and 81.4-83.8%, respectively. In patients with recurrent or metastatic PCa (Cohort B), sensitivity and PPV ranged from 92.9-98.6% (lower bound of95% CI: 84.0-91.6%) and 81.2-87.8%, respectively.

1.6.1.6 Safety Results

A total of 385 subjects received a median dose of 9.14 (6.4-10.5) mCi of ^{18}F-DCFPyL Injection in PyL2301. Overall, ^{18}F-DCFPyL was safe and well-tolerated by all dosed subjects. A total of 81 treatment-emergent adverse events (TEAEs) were reported in 51 (13.2%) subjects. A total of 5 subjects (1.3%) experienced TEAE(s) that were 2: Grade 3 in severity; all were Grade 3 and no subjects experienced Grade 4 or 5 adverse events. The incidence ofTEAEs that occurred in 1% or more of subjects are presented in Table 9.

Table 9: Incidence of Treatment-Emergent Adverse Events that occurred in 1% or more of subjects (N = 385)*

Adverse Event by Preferred Term	Subjects (N=385), n (%)	Events, n
Fatigue	5 (1.3)	5
Dysgeusia	10 (2.6)	
Headache	9 (2.3)	11

*Data as ofNovember 17, 2018

Seven serious adverse events (SAEs) have been reported within the protocol-specified period in subjects who received any amount of ^{18}F-DCFPyL. All of the SAEs were assessed as unrelated to study drug. A tabular summary is provided in Table 10. There were no deaths or AEs that led to study discontinuation.

Table 10: Cumulative Tabulation of Serious Adverse Events (SAEs) in Subjects Who Received Any Amount of ^{18}F-DCFPyL*

Subject Number	Age	Preferred Term	Verbatim Term	Outcome	Causality
102-404	76	Hyperkalemia	Hyperkalemia	Resolved	Not related
104-412	76	Atrial fibrillation	Atrial fibrillation withRVR	Resolved with sequelae	Not related

104-482	62	Spinal cord compression	Pain secondary to spinal cord compress10n	Resolved	Not related
104-485	76	Lower gastrointestinal hemorrhage	Lower gastrointestinal hemorrhage	Resolved with sequelae	Not related
200-406	69	Pyelonephritis acute	Acute pyelonephritis	Resolved	Not related
200-409	59	Coronary artery disease	Cardiac ischemia	Resolved with sequelae	Not related
102-112	66	Coronary artery disease	CAD	Resolved	Not related

*Data as of November 17, 2018

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

To determine the positive predictive value (PPV) of ^{18}F-DCFPyL Positron Emission Tomography (PET) on a per-patient basis in men diagnosed with prostate cancer with increasing PSA levels.

2.1.1 Primary Endpoint

Positive predictive value (PPV) of ^{18}F-DCFPyL PET (per-patient): Number of true positives (TP) divided by number of TP plus number of false positives (FP) as detailed in Section 3.5.1.

2.2 SECONDARY OBJECTIVE

To determine the PPV of ^{18}F-DCFPyL PET on a per-region basis, specifically focusing on the prostate or prostate bed, pelvis, extra pelvis, and bones.

2.2.1 Secondary Endpoint

Positive predictive value (PPV) of ^{18}F-DCFPyL PET on a per-region basis as detailed in Section 3.5.1.

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

3.1.1 Description

This is an interventional, single group assignment, prospective non-randomized, open label Phase 2 trial designed to evaluate the positive predictive value of ^{18}F-DCFPyL PET imaging in men diagnosed with prostate cancer with increasing PSA levels. Eligible patients will undergo baseline assessments according to the Schedule of Study Activities in Appendix A. Approximately 300 participants are planned for enrollment in this study. Patients will receive a single dose of ^{18}F-DCFPyL PET and undergo a PET imaging study.

The PET imaging maybe repeated at a later date if the biopsy of the lesion is negative and if the lesion is present on follow-up imaging. This is outlined in the Study Schematic in Appendix B.

3.2 SELECTION OF STUDY POPULATION

3.2.1 Inclusion Criteria

To be eligible to participate in this trial, subjects must meet all of the following criteria:

- Histologically confirmed diagnosis of prostate cancer
- Biochemical recurrence was defined as a PSA of 0.2 or more ng/mL measured more than 6 weeks after prostatectomy or a PSA of 2 or more ng/mL rise above nadir following radiation therapy (ASTRO Phoenix consensus definition) [59]
    - If PSA values are reported in double decimal points, it will be rounded to the nearest single value decimal point (e.g., 0.14 will be rounded to 0.1 and 0.15 -0.19 will be rounded to 0.2)
- Age 2: 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status::; 2 (Kamofsky 2: 60%)
- Ability to understand and willingness to sign a written informed consent document
- Willing to comply with clinical trial instructions and requirements

3.2.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- History of another active malignancy within 3 years, other than basal cell and squamous cell carcinoma of the skin
- Presence of prostate brachytherapy implants unless approved by the PI
- Administration of another radioisotope within five physical half-lives of trial enrollment
- Radiation or chemotherapy within 2 weeks prior to trial enrollment
- Estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m2
- Serum total bilirubin > 3 times the upper limit of normal

- Aspartate transaminase (AST) or alanine aminotransferase (ALT)> 5 times the upper limit of normal
- Inadequate venous access
- Claustrophobia or any other condition that would preclude PET imaging
- Patients must not be receiving ADT except per criteria directly below. Patients who received in the past must have a serum testosterone that is recovered to at least 100 ng/dL.
    - Patients who have been on ADT +/- novel hormonal agent (NHA) and developed M0CRPC.

3.2.3 Removal of Patients from Study

3.2.3.1 Patient Withdrawal or Early Termination

Patients could choose to discontinue from the study at any time, for any reason, specified or unspecified, and without prejudice.

Patients could be discontinued from the study for any of the following reasons:

- Patient decides to withdraw from the study
- Intercurrent illness that prevents imaging test
- Unacceptable adverse event that may be directly related to the protocol intervention
- General or specific changes in the patient's condition that render the patient unacceptable for an imaging test, in the judgment of the investigator
- Does not meet inclusion/exclusion criteria
- At the discretion of the Sponsor, if deemed appropriate, for any reason

3.2.3.2 Planned Follow-up for Discontinued Patients

Participants have the right to withdraw from the study at any time for any reason. A participant's withdrawal from the study will not jeopardize the relationship with their healthcare providers or affect their future care. This decision must be recorded in writing at the study site.

Should a participant decide to withdraw, all efforts will be made to complete and report the protocol defined study observations as completely as possible and to determine the reason for withdrawal.

3.3 INVESTIGATIONAL PRODUCT

3.3.1 Identity of Investigational Product: ^{18}F-DCFPyL Injection

^{18}F-DCFPyL Injection is an ^{18}-Fluorine-labeled small molecule that targets the extracellular domain ofPSMA. ^{18}F-DCFPyL Injection is labeled with ['^{8}F] fluorine that decays by positron (P+) emission to ['^{8}0] oxygen and has a half-life of 109.77 minutes. The appearance of the ^{18}F-DCFPyL Injection drug product is clear and free of visible particulate matters with a pH of 4.5-7.5. ^{18}F-DCFPyL Injection is a sterile, clear particle-free solution supplied at a specific activity of at least 1000 mCi/µmol at the Time of Administration (TOA), and a radioactivity concentration (RAC) of 1-90 mCi/mL at the Time of Calibration (TOC). The TOC is at the end of synthesis (EOS). The recommended dose of ^{18}F-DCFPyL is 9 mCi in a volume of :S 10 mL administered intravenously in a single injection. The chemical mass dose of carrier DCFPyL is less than 4 µg. The dosage range will be between 7 - 9 mCi .

3.3.2 Packaging and Labeling

Detailed information on the formulation, appearance preparation and labeling procedures can be found in the attached Investigator's Brochure and in the Package Insert provided by the manufacturer for the ^{18}F-DCFPyL Injection.

3.3.3 Receiving, Storage, Dispensing, and Return

3.3.3.1 Receipt of Drug Supplies

The ^{18}F-DCFPyL Injection product contains radioactive material and should only be handled by personnel trained and experienced in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use are limited to a facility licensed by the Federal or State office for Radioactive Substances. Therefore, following release of the final drug product by the cGMP-compliant PET production facility, each unit-dose of ^{18}F-DCFPyL Injection for intravenous injection will be delivered to the PET nuclear medicine laboratory at the respective investigational site.

3.3.3.2 Storage and Handling

Following receipt of the ^{18}F-DCFPyL Injection product, qualified personnel will ensure that the study drug is delivered in good condition, inventoried, labeled, stored at room temperature, and administered by the labeled expiration time (10 hours from the EOS). ^{18}F-DCFPyL Injection must not be diluted. The drug product contains radioactive material and should only be handled by personnel trained and experienced in the use of radioactive isotopes with proper shielding and monitoring.

3.3.3.3 Dispensing of Study Drug

The drug should be labeled and dispensed in compliance with the pharmacy manual, all regulatory agencies, and the investigator physician's prescription order. The 18F-DCFPyL dose will be measured by the qualified personnel in a dose calibrator prior to dispensing. Then, the syringe will be placed in a shielded carrier and administered as an intravenous injection. After the dose administration, the qualified personnel (nuclear medicine technologist) will re-assay the syringe for residual tracer activity. Measured radioactivity values and times of measurement will be documented, as well as the total injected volume. Regulatory agencies require the disposition of all investigational drugs received by each clinical site to be accurately accounted for. Information on drug disposition required by law consists of the date received, date dispensed, quantity dispensed, and the patient identification number to whom the drug was dispensed.

3.3.4 Administered Intervention

The dispensed dose will be injected slowly by a qualified nuclear medicine technologist as an IV injection. A dose of 9 mCi (333 MBq) or less ^{18}F-DCFPyL injection will be administered via an in-dwelling catheter placed in an antecubital vein or an equivalent venous access. The drug product contains radioactive material and should only be handled by personnel trained and experienced in the use of radioactive isotopes with proper shielding and monitoring.

3.3.5 Selection of Dose in the Study

The intervention is a PET scan with the radiolabeled PSMA ligand ^{18}F-DCFPyL. Prior to the first-in-human study with PyL (Study Jl418) at JHU, human dosimetry was extrapolated from a preclinical biodistribution study in xenograft mice.[55] The mouse organ activity concentrations in ¾ID/g were converted to the human %ID/organ by setting the ratio of organ ¾ID/g to whole-body ¾ID/gin the mouse equal to that in humans and then solving for the human %ID/organ. The adult male phantom organ masses listed in the OLINDA/EXM 1.0 were used for the conversion. The human source organ time-activity curves were fitted using a monoexponential function.

Because the biodistribution data were radioactive decay-corrected, only the biological removal constants were obtained from the curve fits, and the physical decay constant for F-^{18} was added in obtaining the time-integrated activity coefficients (TIAC). The source organ TIACs in MBq-h/MBq were entered in the OLINDA/EXM 1.0 for the dose calculations. The dynamic voiding bladder model was used to obtain the TIAC for the urinary bladder contents. The whole-body clearance half-life (obtained as the sum of sampled tissues, excluding the tumors) was used as the half-life to describe urinary bladder filling. All radioactivity was assumed to be eliminated via the urine. A one-hour voiding interval was assumed.

The estimated human organ exposure values are presented in Table 3. The urinary bladder wall was projected to be the organ with the highest absorbed dose. To limit the radiation-absorbed dose to the urinary bladder in accordance with 21 Code of Federal Regulations (CFR) § 361.1 (:S 50 mGy), the highest human dose is estimated to be 8.95 mCi. As a result,

the first-in-human dose used at JHU for obtaining basic information regarding the metabolism (including kinetics, distribution, and localization) was determined to be :S *9* mCi. The *9* mCi administered dose of ^{18}F-DCFPyL Injection is comparable to the radiation dose of other radiotracers used in oncology such as [^{18}F]-FDG.

3.3.6 Selection and Timing of Dose for Each Subject

This is an open-label study. All eligible patients will receive a single dose of the investigational agent. All patients will receive a single intravenous dose, *9* mCi (333 MBq) or less (range between 7 - *9* mCi) of ^{18}F-DCFPyL Injection.

3.3.7 Procedures for Ensuring Subject Compliance

This is an open-label study. All eligible patients will receive a single dose of the investigational agent; therefore, no compliance measures are required.

3.3.8 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All eligible patients will receive the investigational agent.

3.3.9 Investigational Product Accountability

3.3.9.1 Investigational Product Inventory Records

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of receipt of investigational product will be documented according to the PI's requirements. An investigational product accountability log will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the destruction of all investigational product.

3.3.9.2 Return or Destruction of Investigational Product

The Investigator is responsible for accounting for all unused study product and destroying all used study product containers in compliance with. At the conclusion of the study, or other situations as applicable (ex. site closure, IP expiry, etc.) the Investigator must agree to return or destroy all study materials as instructed by the package insert. Unused or residual waste should be disposed of as radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidance.

3.3.10 Blinding

This study is a single-dose, open-label study. No blinding procedures will be used. No subjects will be blinded.

3.4 SCHEDULE OF STUDY ACTIVITIES

The time the imaging test will be performed relative to dosing is shown in the Schedule of Study Activities (Appendix A).

3.5 ASSESSMENT OF INTERVENTION

3.5.1 Imaging Protocol and Follow up

Patients will be intravenously injected with:::::; 333 MBq (:::::; 9 mCi) of radiotracer approximately 60 minutes prior to image acquisition and will be imaged using the GE Discovery PET-CT scanner at UPMC Hillman Cancer Center, UPMC Magee-Women's Hospital, or UPMC Shadyside Hospital. The scanner will be operated in three-dimensional (3D) emission mode on CT attenuation correction as the case may be and images will be reconstructed with manufacturer-supplied ordered subset expectation maximization iterative methods without point-spread function. The field of view for ^{18}F-DCFPyL PET scans will be vertex to mid-thigh.

The PET images will be evaluated qualitatively by UPMC Hillman Cancer Center (HCC) nuclear medicine physicians. PET scans will be randomly assigned between five PET readers. Interpreters will have at least more than 5 years of PET interpretation and will interpret images. Double reading will be performed for all the PET scans. The readers will be provided with the recent PSA levels and the type of primary therapy (prostatectomy vs radiation therapy) but will be blinded to all other information. The report will indicate the localization of detected lesions either in the prostate bed, locoregional lymph nodes, distant lymph nodes, bones, and/or visceral organs. A scan will be deemed 'positive' if at least one lesion suggestive of disease recurrence is noted. Prostate lesions and lymph nodes will be considered positive if the uptake in those lesions exceeds blood pool activity. Bone lesions will be recorded as positive if the activity is higher than normal bone marrow uptake.

The UPMC HCC nuclear medicine physicians have extensive experience in interpreting FDG-PET/CT scans including those performed with a variety of agents currently used in the research setting. Scans will be interpreted using HE AW 3.2 Volume Viewer software package.

Visual interpretation:

1. Lymph nodes will be deemed positive if the PET scan uptake is focal and greater than blood pool (adjacent or mediastinal blood pool). Pelvic lymph nodes will be subclassified

according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups).

2. Visceral lesions will be considered positive if the uptake is focal and greater than physiologic background activity of the involvement organ or the anatomic location.
3. Bone lesions will be considered positive if the uptake is focal and greater than normal marrow uptake.
4. Prostate bed and prostate lesions will be considered positive if uptake is focal and greater than background activity of the prostate.

Follow-up imaging:

A chart review will be performed at 3, 6, 9 and 12 months with a plan to communicate with the referring oncologist team regarding the plan for follow-up imaging with a CT, MRI and/or bone scan. If a follow-up imaging is not obtained by 12 months, then imaging will be requested. Interpretation of follow-up imaging will be performed by local read. The follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons.

PET positive findings will be validated as true or false positive as outlined in more detail below. False negative ^{18}F-DCFPyL PET findings cannot be determined as this would require biopsies of all PET negative lesions that are present on conventional imaging.

^{18}F-DCFPyL PET validation will be based on follow-up imaging:

1. Lymph nodes will be assessed by change **in** size. PET positive lymph nodes will be considered:
   a. True positive:
      - If on follow-up imaging within 3-12 months, lymph nodes seen on CT or **MRI** scan decrease by more than 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).
      - If patients with solitary lymph node regions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and the lymph nodes do not change in size (less than 30% decrease or less than 20% increase in short axis diameter).

   b. False positive:
      - If on follow-up imaging within 3-12 months, sites of initial ^{18}F-DCFPyL PET positive lymph node lesions seen on CT or MRI scan decrease by more than 30% without systemic therapy or focal therapy at this site.

- If PET positive lymph node lesions do not meet the criteria for above false positive or true positive findings.

2. Visceral lesions (non-lymph node soft tissue or organ) will be assessed by change in size. PET positive visceral lesions will be considered:
   a. True positive:
      - If on follow-up imaging within 3-12 months, visceral lesions seen on CT or MRI scan decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.
      - If patients with solitary visceral metastasis show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

   b. False positive:
      - If on follow-up imaging within 3-12 months, sites of initial PET positive lesions seen on CT or MRI scan decrease by more than 30% without systemic therapy or focal therapy at this site.
      - If ^{18}F-DCFPyL PET positive lesions do not meet the criteria for above false positive or true positive findings.

3. ^{18}F-DCFPyL PET positive bone lesions will be considered:
   a. True positive:
      - If there was a corresponding positive sclerotic lesion on the CT portion of the ^{18}F-DCFPyL PET in the same location as the focal uptake.
      - If there is focal uptake seen on the baseline bone scan performed within one month of ^{18}F-DCFPyL PET.
      - If there is a lesion noted on the initial MRI imaging scan performed within one month of ^{18}F-DCFPyL PET.
      - If within 12 months follow-up CT scan demonstrates development of sclerosis.
      - If within 12 months follow-up MRI scan demonstrates a new bone lesion.
      - If within 12 months follow-up bone scan demonstrates new focal uptake.

   b. False positive:
      - If ^{18}F-DCFPyL PET positive bone lesions do not meet the criteria for true positive findings.

4. ^{18}F-DCFPyL PET positive prostate bed and prostate lesions will be considered:
   a. True positive:
      - If on follow-up imaging within 12 months, lesions seen on CT or MRI scan decrease by 30% (for patients undergoing systemic treatment of focal therapy at this site) or increase by 20% in largest diameter.

- If patients with prostate bed lesions show a decrease of PSA by greater than 50% after targeted treatment (i.e. external beam radiation) and lesions do not change in size (less than 30% decrease or 20% increase in largest diameter).

b. False positive:
   - If on follow-up imaging within 3-12 months, sites of initial ^{18}F-DCFPyL PET positive lesions seen on CT or **MRI** scan decrease by more than 30% without systemic therapy or focal therapy at this site.
   - If ^{18}F-DCFPyL PET positive lesions do not meet the criteria for above false positive or true positive findings.

Histopathology/Biopsy:

1. Localization of lesions for histopathology/biopsy will be classified according to the regions in table (Definition ofregions) below.
2. The ^{18}F-DCFPyL PET positive findings will be targeted to be confirmed by histopathology/biopsy if and whenever clinically feasible.
3. Histopathological procedures, biopsies and follow-up imaging will be performed as clinically indicated and as per the standard of care/institutional protocol. The following elective procedures may guide the investigator:

   A. Positive HP/Biopsy: Confirmed sites of metastatic or tumor involvement by histopathology/biopsy will be discussed with the responsible physician/surgeon.
   B. Negative Biopsy: Patients with suspected tumor recurrence on the PET with negative histopathology/biopsy will be handled as outlined below:

      1. Lymph nodes:
         - For patients undergoing nodal dissection: Patients will be rescanned with dedicated CT or MRI scan, if clinically feasible, to determine if the suspicious ^{18}F-DCFPyL PET positive node was removed.
            - If PET positive lymph node is still present, a repeat biopsy can be pursued if clinically feasible and applicable, or follow-up using imaging as described above will be performed.
            - If the corresponding node was removed, then this will be considered a False Positive.
         - For patients undergoing needle biopsy: Images of the procedure will be reviewed to determine if the correct node was biopsied.
            - If the correct node was biopsied, then a negative biopsy will be considered a False Positive.
            - If the incorrect node was biopsied, then follow-up imaging as described above will be performed if clinically feasible.

11. Bone lesions: Given the high rate of false negative biopsies for osseous metastases in patients with prostate cancer, patients with negative bone biopsies of PET positive lesions will be further evaluated:
    - If pathology demonstrates alternative diagnoses that is known to be PET positive (e.g. Renal Cell Carcinoma metastases, Paget's disease), then this will be considered a False Positive.
    - If pathology is indeterminate, then follow-up imaging as described above will be performed to determine if the lesion is a True Positive or False Positive.

111. Additionally, a repeat ^{18}F-DCFPyL PET may also be obtained as per treating physician discretion in addition to repeat conventional imaging (CT and/or MRI) in cases of negative biopsy to determine if the biopsy was true negative or false negative.

C. Although not routinely performed during standard practice, immunohistochemical or specimens (primary and lymph node metastases) may be performed, although not required.

Table: Definition of regions

Region	Description
1	Prostate bed
2	Pelvis outside of prostate bed (including LNs)
3	Extra-pelvic soft tissue lesions, LNs, visceral metastases
4	Osseous metastases

3.5.2 Screening Assessments

Patients determined to meet the eligibility criteria to participate in the study will undergo Screening assessments as per the Study Schedule of Activities in Appendix A. The following screening procedures will be performed:

- Informed Consent will be obtained prior to any study-related procedures
- Eligibility assessment per the inclusion and exclusion criteria and diagnosis confirmation
- Subject demographics
- Prostate cancer history
- Vital Signs

- Physical examination, including height, weight, body mass index (BMI) and ECOG performance status assessment
- List of concomitant medications (hormonal agents only)
- Lab assessments

3.5.3 Procedure for Registration of Subjects

Patients must not start study activities prior to registration. Subjects can be enrolled after eligibility criteria are met. Registration will require the following information:

- Date of consent
- Participant's name
- Date of birth
- Primary study physician
- Confirmation of eligibility

3.6 ASSESSMENTS DURING INTERVENTION

3.6.1 Demographic and Medical Record Review

3.6.1.1 Patient Demographics

For this study, demographic information will be reviewed at the Screening Visit and include:

- Date of birth
- Sex
- Self-reported race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Pacific Islander, Caucasian, or other)
- Self-reported ethnicity (Hispanic/Latino or Not Hispanic/Latino)

3.6.1.2 Prostate Cancer History

Medical history related to diagnosis to be recorded for each patient consists of:

- Height
- Weight
- Clinically significant diseases
- Surgeries
- Cancer history (including prior cancer therapies and procedures)
- Prior medications (hormonal agents only)

These elements are considered as HIPAA identifiers and will be listed individually in the HIPAA authorization portion of the consent form.

3.6.1.3 Physical Examination

The physical examination will include routine examinations, not including rectal or genitourinary examinations. All clinically significant abnormalities will be recorded in subject's medical record and on the physical exam CRF page. Any abnormality that, in the opinion of the Investigator, is relevant to the safety of the subject or could impact safety or efficacy results for the subject will be considered as "clinically significant". After administration of the first dose of study treatment, each physical exam abnormality that is clinically significant will be recorded as an AE. A complete physical includes an evaluation of the:

- Head, eyes, ears, nose, and throat
- Dermatological
- Musculoskeletal
- Respiratory
- Gastrointestinal
- Genitourinary
- Neurological systems

Any abnormality identified at baseline should be recorded on the general medical history and baseline conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

3.6.2 Interventional Examination

During the administration of the study drug, the following assessments will be reviewed:

- Concomitant medications
- Adverse event review (post-injection)

3.7 FOLLOW UP ASSESSMENTS

Following the administration of the study, there will be a post-study follow period and a long term follow up period.

3.7.1 Post-Study Follow Up

For the initial seven days after study drug administration, the following will be reviewed:

- Concomitant medications
- Adverse events

3.7.2 Long Term Follow Up

After the post-study follow up period, the participant will continue to be followed as described in section 3.5.1 Imaging Protocol and Follow Up.

3.8 ASSESSMENT OF SAFETY

3.8.1 Safety evaluation

Patients will be monitored during infusion of ^{18}F-DCFPyL and for 120 minutes after the infusion. The safety and tolerability of ^{18}F-DCFPyL Injection will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events up to 7 days following infusion

3.8.2 Radiation exposure from PSMA PET imaging

As part of this scan there is radiation delivered from the ^{18}F and from the low dose CT or MRI scan that are performed as part of the PET imaging for attenuation correction and co-registration. Although any exposure to ionizing radiation has the potential to cause some harm to tissue, the radiation exposures in this study are comparable to the low-level exposures associated with common diagnostic procedures such as PET/CT scanning. There remains a low theoretical risk of developing a cancer at some point later in life as a result of the radiation exposure received in this study. This risk is much smaller than the clinical risks posed by the patient's current cancer or the salvage radiation therapy the patient might have received or will be receiving. The dose selection process described in section 3.3.5 was aimed at limiting the radiation-absorbed dose to the urinary bladder in accordance with 21 Code of Federal Regulations (CFR) § 361.1 ('.S 50 mGy). Consequently, the 9 mCi administered dose of ^{18}F-DCFPyL Injection is comparable to the radiation dose of other radiotracers used in oncology such as [^{18}F]-FDG. The dose range for ^{18}F-DCFPyL will be 7 - 9 mCi. The approximate Effective Dose for a whole-body attenuation correction CT would be 0.05 rem.

3.8.3 Adverse Events

3.8.3.1 Definition of Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this imaging test. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

For this study, AEs are regarded as "intervention emergent," if they occur after study drug has been administered.

Pre-planned or elective surgeries or therapies should be recorded in the patient's source documents but are not to be considered AEs unless there was any change to the patient's medical condition during the AE collection period.

Collection of AEs will occur upon signature of consent.

3.8.3.2 Definition of Serious Adverse Events

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE. SAE reporting is required as soon as the participant signs consent.

SAE reporting is required during the 30-day follow up period after the participant's investigational intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

SAE reporting will comply with UPMC HCC SOPs and with local and federal regulations.

3.8.3.3 Evaluation of Adverse Events Seriousness

The seriousness must be determined for each AE, according to the criteria given.

Intensity/Severity

The intensity of an AE is classified according to NCI-CTCAE version 5.0, considering the possible range of the intensity of the event:

- NCI-CTCAE Grade 1 (mild)
- NCI-CTCAE Grade 2 (moderate)
- NCI-CTCAE Grade 3 (severe)
- NCI-CTCAE Grade 4 (life-threatening)
- NCI-CTCAE Grade 5 (fatal)

Study drug action

AEs requiring any action, i.e. medication or therapy for treatment, should be treated according to recognized standards of medical care to protect the health and well-being of the patient.

3.8.3.4 Relationship to Study Intervention

Causal relationship to study drug

The possible causal relationship between the AE and the administration of the study agent is classified according to the following question:

"Is there a reasonable likelihood that the event was caused by the study drug?"

Possible answers are:

- Definitely Related: Plausible time relationship to the administration of IMP/RP. There is no plausible explanation by underlying/concurrent disease or other drugs/events.
- Probably Related: Plausible time relationship to the administration of **IMP/RP,** and a respond to dechallenge of IMP/RP.
- Possibly Related: Plausible time relationship to the administration ofIMP/RP, but the AE can be also plausibly explained by the underlying/concurrent disease or other medicinal products/events.

- Unlikely Related: Minimal plausible relationship to the administration of IMP/RP. Other medicinal products, events, and the underlying/concurrent disease provide a plausible explanation.
- Unrelated: No plausible relationship to the administration of IMP/RP. There is clear evidence that the AE is not connected to the IMP/RP administration.

Causal relationship to study conduct
The possible causal relationship between the AE and any study-conduct-related procedures and activities required by the protocol is classified according to the following question:

"Is there a reasonable likelihood that the event was caused by the study conduct?"

3.8.3.5 Expectedness

Expected Conduct-related AEs

The use of an indwelling cannula for the administration of study drug may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable.

Patients may also experience discomfort from lying in the camera, e.g. back pain.

Expected Adverse Drug Reactions

The definition below follows ICH-GCP (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting):

Adverse drug reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered as ADR. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction is defined as any adverse drug experience, the nature, specificity or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product). "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product.

3.8.3.6 Assessment and Documentation of Adverse Events

At every assessment time point during the study until end of the study, the patient will be asked a non-leading question such as "Have you had any health problems since you were last asked/ since your last visit?"
All AEs reported in response to questioning, as well as AEs reported spontaneously and occurring at any other time, will be recorded on the 'adverse event' page(s) in the CRF, regardless of causality.

If an AE fulfills any of the SAE criteria, both the AE pages of the CRF and the Serious Adverse Event Form must be completed.

SAEs are recorded for the entire duration of the study.

For both serious and non-serious AEs, documentation must be supported by an entry in the patient's hospital notes.

REPORTING OF SERIOUS ADVERSE EVENTS

All events meeting the definition of a serious adverse event should be reported according to the departmental SAE checklist and SAE form. SAE reporting is required from the time of the participant's first dose of investigational product until 30 days after the last dose of treatment or intervention. Any events that occur greater than 30 days after last dose that are at least possibly related to treatment must be reported. The initial SAE form should be sent to the following within 24 hours/I business day of the Principal Investigator becoming aware:

1. Investigator
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- Current status of study drug
- All interventions to address the AE (testing and result, treatment and response)
- Hospitalization and/or discharge dates
- Event relationship to study drug

FOLLOW-UP REPORTS
Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

3.8.4 Review of Safety Information: Sponsor Responsibilities

The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

Sponsor-investigators of IND applications are subject to compliance with both the adverse reaction reporting requirements of the Sponsor and the adverse event reporting requirements of the Investigator.

3.8.5 IND Safety Reports

The sponsor must notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under **Sections 3.8.5.1 to 3.8.5.4 below.** In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

3.8.5.1 Serious and unexpected suspected adverse reaction

The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events

that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

3.8.5.2 Findings from other studies

The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under section **3.8.5.1),** whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug. Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

3.8.5.3 Findings from animal or in vitro testing

The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure. Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.

3.8.5.4 Increased rate of occurrence of serious suspected adverse reactions

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

3.8.6 Submission of IND safety reports

The sponsor must submit each IND safety report in a narrative format or on Form FDA 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation, and organization of files). The sponsor may submit foreign suspected adverse reactions on a Council for International Organizations of Medical Sciences (CIOMS) I Form instead of a Form FDA 3500A. Reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division in the Center for Drug Evaluation and Research or in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. Upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

3.8.6.1 Unexpected fatal or life-threatening suspected adverse reaction reports

The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

3.8.6.2 Reporting format or frequency

FDA may require a sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the FDA review division that has responsibility for review of the IND.

3.8.6.3 Investigations of marketed drugs

A sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND is required to submit IND safety reports for suspected adverse reactions that are observed in the clinical study, at domestic or foreign study sites. The sponsor must also submit safety information from the clinical study as prescribed by the post marketing safety reporting requirements.

3.8.6.4 Reporting study endpoints

Study endpoints (e.g., mortality or major morbidity) must be reported to FDA by the sponsor as described in the protocol and ordinarily would not be reported under Section 3.8.7 third bullet of this section. However, if a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis), the event must be reported under *Serious and unexpected suspected adverse reaction* as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality).

3.8.7 Follow-up

- The sponsor must promptly investigate all safety information it receives.
- Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report."
- If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under the IND safety reports section is so reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

3.8.8 Disclaimer

A safety report or other information submitted by a sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse event. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse event.

The principal investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

3.8.9 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Sponsor-Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s);* 2) *serious;* and 3) *unexpected.* Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) *associated with the investigational drug or study treatment(s);* 2) *fatal or life-threatening;* and 3) *unexpected* will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Sponsor-Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

3.9 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. These are described in the following sections.

3.9.1 Data Collection, Monitoring, and Transfer

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data including adverse events, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the Clinical Trial Management Application (CTMA), a 21 CFR Part 11-compliant data capture system provided by the UPMC HCC Clinical Research Services (CRS). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

3.9.2 Quality Control and Quality Assurance

The PI will perform a clinical review to define the level of resolution required of each data field, with major safety fields (e.g., AE) given the highest importance. The database will be 100% verified against the CRFs. A clinical review will be performed by the PI to identify those minor issues that could remain unresolved.

3.9.3 Data and Safety Monitoring Plan

Investigators, Sub-investigators and clinical research staff meet regularly to review in disease center Data Safety Monitoring Boards **(DSMB)** to review and discuss study data to include, but not limited to, the following:

- Serious adverse events
- Subject safety issues
- Recruitment issues
- Accrual
- Protocol deviations
- Unanticipated problems
- Breaches of confidentiality

Minutes from disease center DSMB meetings are available to those who are unable to attend.

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI CTCAE version 5.0 and recorded prior to each course of the investigational therapy. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB and FDA. Any modifications necessary to ensure patient safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The disease center will forward a summary of the DSMB to the UPMC Hillman Cancer Center DSMC which meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly by the disease center DSMB.

Both the UPMC HCC DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a double locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

3.10 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

3.10.1 Study Design

This is a single arm phase II clinical trial to evaluate the positive predictive value (PPV) of ^{18}F-DCFPyL PET imaging in men diagnosed with prostate cancer with increasing prostate-specific antigen (PSA) levels. PPV is the number of true positives (TP) divided by number of patients who are tested positive (i.e., TP + FP) based on the PET imaging. The determination ofTP and positive testing is detailed in Section 3.5.1. Secondary endpoints are PPV of ^{18}F-DCFPyL PET (per-region). All patients who are diagnosed with prostate cancer with increasing PSA levels and who have received PET scans will be evaluable for the analysis.

All patients will be followed up for histopathologic analysis, conventional imaging (CT, MRI and/or bone scan) and/or serum PSA after focal salvage therapy acquired during clinical routine. Combination of (in descending priority) histopathologic analysis, imaging, and PSA follow-up after local/focal therapy will used for lesion validation. Validation will be performed by the unblinded local investigators after reviewing images and reports, following prespecified criteria of the study protocol. In patients with follow-up, positive ^{18}F-DCFPyL PET findings will be validated as true or false-positive results. Region negative on ^{18}F-DCFPyL PET, but with subsequently confirmed prostate cancer by histopathologic analysis, will be considered false-negative results. True negative will not be defined. (please see section 3.5.1. for details).

3.10.2 Sample Size

A total of 300 evaluable participants will be enrolled into this study. We expect approximately 85% of them, i.e., 255 patients, will have positive test results. Based on these 255 patients, the exact 95% confidence interval (CI) for PPV has a width ofless than 12%. The following table shows the exact 95% CI corresponding to different observed PPV values.

Observed PPV	**95% CI of true underlying PPV**
80%	**(75%, 85%)**
84%	**(79%, 88%)**
88%	**(84%, 92%)**
92%	**(88%, 95%)**
96%	**(93%, 98%)**
100%	**(99%, 100%)**

As an example, from this table, an observed 80% PPV value indicates that we can be 95% confident that the true underlying PPV lies in the interval (75%, 85%). If the observed PPV is 88%, then we can be 95% confident that the true underlying PPV lies in the interval (84%, 92%).

3.10.3 Analysis of Primary and Secondary Endpoints

PPV will be estimated by the number of true positives (TP) divided by number of patients who are tested positive (i.e., TP + FP) based on the PET imaging, with the corresponding exact 95% confidence intervals (Cis) being reported. The determination ofTP and positive testing is detailed in Section 3.5.1. Secondary endpoints are the PPV of ^{18}F-DCFPyL PET (per-region). These will also be estimated as the corresponding percentage and its exact 95% Cis.

The safety profile observed to date suggests that the toxicity of the proposed study product is unlikely to be clinically significant. However, we will monitor toxicity closely. Any patient who has started the studied treatment will be evaluable for safety. The NCI CTCAE version 5.0 defines the term toxicity as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

3.10.4 Missing Data

Missing data will not be imputed except for AE and CONMED missing dates.

3.10.5 Interim Analyses

There is no Data Safety Monitoring Committee or Interim Analysis planned for this study.

4. ETHICS

4.1 COMPLIANCE STATEMENT

The study will be conducted in accordance with the protocol, Good Clinical Practices, the relevant ICH guidelines, the applicable regulatory requirements, and the ethical principles that have their origins in the Declaration of Helsinki. As required by the US Food and Drug Administration (FDA) Code of Federal Regulations (CFR) (21 CFR 56) and the Declaration of Helsinki, the study protocol, amendments, and Informed Consent form will be reviewed and approved, according to 21 CFR §50 and §56, respectively, by the study center's IEC or IRB.

4.2 SUBJECT INFORMATION AND CONSENT

Before protocol-specific procedures are carried out, qualified consenting professionals will explain full details of the protocol and study procedures, as well as the risks involved to patients prior to their inclusion in the study. Patients will also be informed that they are free to withdraw from the study at any time.

All patients must sign an !RB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the **IRB** of record. Both the patient and the qualified consenting professional will sign the consent form. The patient must receive a copy of the signed informed consent form.

5. PUBLICATION POLICY

The Investigator will refer to the Investigator agreement and clinical trial agreement for the publication and disclosure policy.

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7. APPENDICES

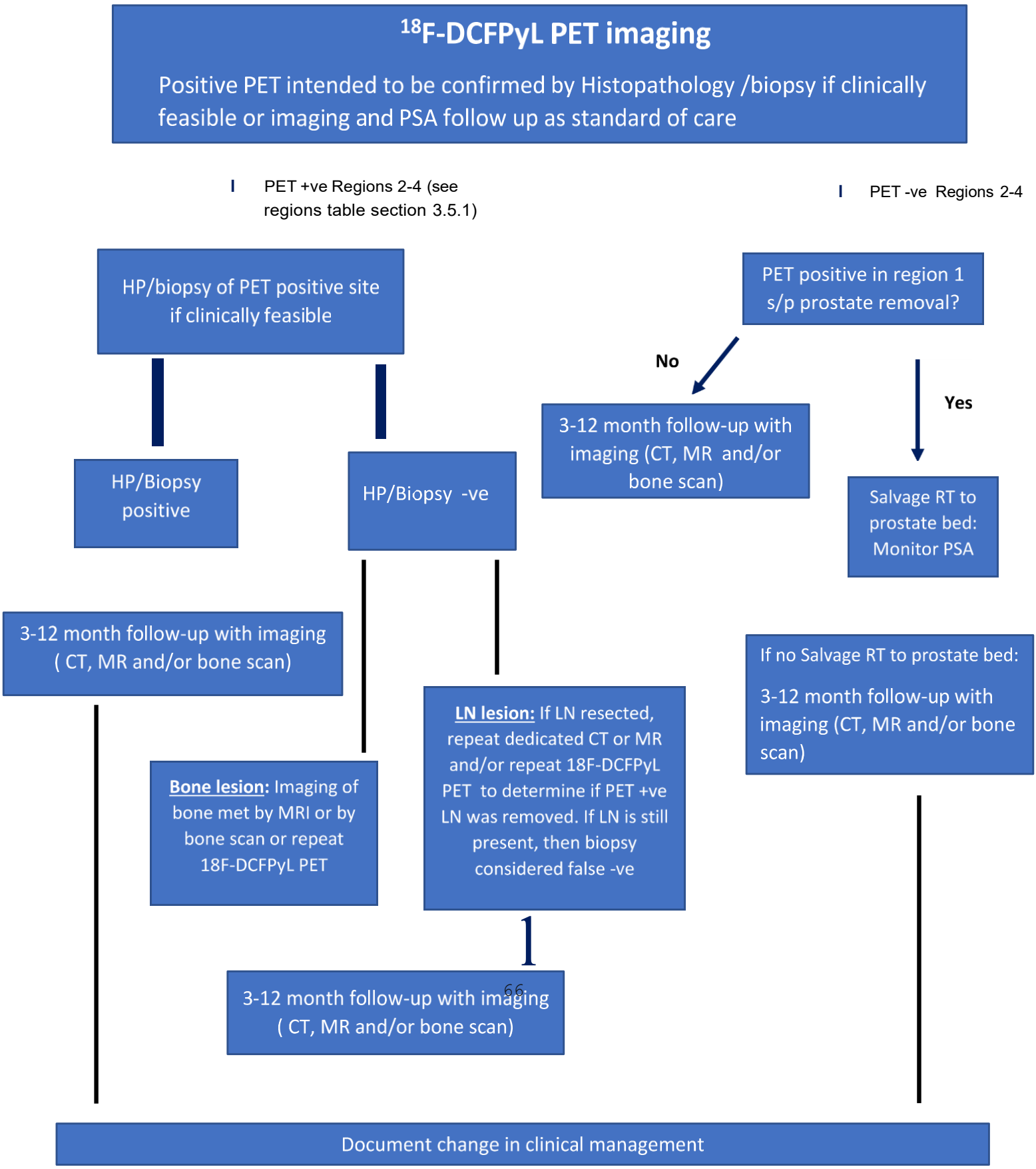
7.1 APPENDIX A: SCHEDULE OF STUDY ACTIVITIES

Visit Type	**Screening**	**Imaging Day - Procedures**	**Imaging Day - Follow-up**	**Post-Study Follow-up**	**Long Term Follow** Upg
Day/Timing	**Within 28 days of imaging**	**Day 1** **(At the time of tracer injection)**	**Day 1** **(120 min post-injection follow-up)**	**Day7** (+/- **2 days)**	**Day 8 to One Year**
Procedures					
Informed Consent	x				
Eligibility	x				
Medical History	x				
Laboratory Assessmentsa	x				
Physical Examb	x				
Vital Signs	x				
Administration of ^{18}F-DCFPyL		x			
PET Imaging Scanc		x			
Patient Concomitant Medicationsd	x	x	x	x	
Adverse Eventse			x	x	
Conventional Imagingf					IX

a. Glomerular filtration rate (eGFR); serum total bilirubin; aspartate transaminase (AST); alanine aminotransferase
b. Physical exam includes a review of height, weight and BMI
c. PET scan will be perfonned approximately 60 minutes after administration of ^{18}F-DCFPyL
d. Only hormonal agents are required to be collected pre-injection; concomitant medications taken for treatment-related adverse events only are required to be collected on Day I post-injection and Day 7

e. Adverse events information related to the injection can be collected via telephone contact
f. Dedicated CT, MRI and/or bone scan; interpretation of follow-up imaging will be performed by a local read
g. Long term follow-up includes chart review for imaging, biopsies, PSA levels and prostate cancer treatment at 3, 6, 9 and 12 months or until patient has responded to treatment

7.2 APPENDIX B: STUDY SCHEMATIC



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