CLINICAL STUDY PROTOCOL

Study Number:	PyL 2301
Study Title:	A Pr**O**spective Phase 2/3 Multi-Center **S**tudy of ^{18}F-DCF**P**yL PET/CT Imaging in Patients with P**R**ostate Cancer: **E**xamination of Diagnostic Accurac**Y** (OSPREY)
Product Name:	^{18}F-DCFPyL INJECTION (PyL)
IND Number	129,952
Sponsor:	Progenics Pharmaceuticals, Inc. One World Trade Center 47th Floor, Suite J New York, NY 10007 (646) 975-2500
Protocol Version	Original: July 12, 2016 Amendment 1: September 16, 2016 Amendment 2: November 6, 2017 NCT02981368

Confidentiality Statement

INVESTIGATOR'S AGREEMENT

I acknowledge that I have read the attached protocol and agree that it contains all information necessary to conduct the study and agree to conduct the study as outlined within.

I agree to comply with all stated provisions, including but not limited to regulations/guidelines relevant to the conduct of human trials, as set forth in Title 21 of the Code of Federal Regulations (CFR), and Good Clinical Practices as set forth by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

I will not initiate the study until I have obtained written approval from the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC). I will obtain written informed consent from all study participants prior to performing any screening procedures.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I understand and acknowledge that confidential information includes, but is not limited to, (i) the study protocol, (ii) the data derived from the study, and (iii) my impressions of the progress or results of the study. I further agree that I will not use such Confidential Information for any purpose other than the evaluation or conduct of the clinical investigation.

I certify that I have not been disqualified by any regulatory authority or otherwise disqualified from serving as a principal investigator. I also agree that in the event I become debarred, I shall immediately cease all activities relating to the study.

I am not presently, nor will I be during the term of the study, a consultant or advisor to any division of any financial or securities firm.

I understand that my signature on a case report form indicates that the data therein have been reviewed and are deemed to be complete, accurate, and acceptable to me.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

SPONSOR SIGNATURE PAGE

Protocol Number: PyL-2301

Protocol Title: 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)

Protocol Version: Amendment 2: November 6, 2017

This Clinical Protocol was subject to critical review and has been approved by the Study Sponsor.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	E-mail and Telephone Number
Clinical Project Manager	[redacted]	
Clinical Study Leader		
Responsible Physician		

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
AUC	area under the time-concentration curve
BP	blood pressure
BUD	beyond use date
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CL	total body clearance
CMP	comprehensive metabolic panel
C_{max}	maximum (peak) serum concentration
CRF	case report form
CT	computed tomography
DMC	Data Monitoring Committee
DoB	date of birth
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Synthesis
FDA	Food and Drug Administration
^{18}F	Fluorine-18
FDG	Fluorodeoxyglucose
^{68}Ga	Gallium-68
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
hr	Hour(s)
HR	Heart Rate

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
JHU	Johns Hopkins University
kg	Kilogram
m	Minute/Meter
mAb	Monoclonal Antibody
MBq	MegaBequerel
mCi	MilliCurie
MDP	methylene diphosphonate bone scan
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
MRT	Mean Residence Time
mSv	millisievert
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
CTCAE	Common Terminology Criteria for Adverse Events
ng	nanogram
nM	nanometer
NOAEL	No Observed Adverse Effect Level
NPV	negative predictive value
PET/CT	positron emission tomography–computed tomography
PI	Principal Investigator
PK	pharmacokinetics

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
PLND	Pelvic lymph node dissection
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
PT	Preferred Term
RBC	Red Blood Cell count
RCC	Renal cell carcinoma
RP	radical prostatectomy
RR	respiratory rate
SAE	Serious Adverse Event
SAP	statistical analysis plan
SD	Standard deviation
SoC/SOC	Standard of Care/System Organ Class
SOP	Standard Operating Procedures
SUV_{max}	Maximum Standardized Uptake Value
SUV_{peak}	Peak standardized uptake value
SUV_r	ratio to reference tissue standardized uptake value
TIAC	Time-Integrated Activity coefficients
US	United States
V_{ss}	Volume of Distribution at Steady State
WBC	White Blood Cell count

3. INTRODUCTION

3.1. Background Information

Prostate cancer is the most common cancer among men in the United States (US) with an estimated number of new cases of 161,360 annually; it also represents the second most common cause of cancer-related death in men.[1] The vast majority of men dying 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), [^{99m}Tc] 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) employing 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG PET), the clinical standard for a number of cancers, has demonstrated mixed results in imaging prostate cancer.[6-9] Other tumor metabolism-based approaches tested in prostate cancer (and other cancers) are the use of labeled choline to take advantage of the increased expression of choline kinase (ChKα) in tumor cells[10], or increased uptake of amino acids such as methionine or leucine. ^{11}C choline was approved by FDA in 2012; however, the sensitivity of ^{11}C choline tends to be limited in extraprostatic lesions.[11-14] Most recently, synthetic L-leucine analog trans-1-amino-3-^{18}F-fluoro-cyclobutane carboxylic acid (^{18}F-FACBC; Axumin®) was approved for use in men with suspected recurrence of prostate cancer.

A number of new, targeted PET tracers have been introduced for imaging prostate cancer.[15-20] Proving particularly effective are low-molecular-weight agents that bind to the prostate-specific membrane antigen (PSMA), which is highly expressed in castration-resistant, metastatic prostate cancer.[21,22,23] A novel, high specific activity, highly selective, low-molecular weight PSMA-targeted PET radiotracer, ^{18}F-DCFPyL, is currently being investigated as an imaging agent for prostate cancer at Johns Hopkins University School of Medicine (JHU). The purpose of the current study is to further the clinical development of ^{18}F-DCFPyL to support marketing approval.

3.2. 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 161,360 new cases of prostate cancer are diagnosed in the US, coupled with approximately 400,000 newly diagnosed cases in Europe.[1,24] It is estimated that the disease will affect one in seven men in their lifetimes, leading to approximately 293,000 deaths per year in developed countries worldwide.[25] The mortality from the disease is second only to lung cancer in men.[1] An estimated $8 billion is currently spent annually in the US on surgery, radiation, drug therapy and minimally invasive treatments.[26]

Several imaging modalities are currently employed for the diagnosis, staging and prognosis of prostate cancer metastases. Conventional cross-sectional imaging with CT and MRI rely on anatomical changes (lesions >1 cm), often resulting in missed lymph node metastases and low

sensitivity. 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 revealed that CT and MRI performed equally poorly in the detection of lymph node metastases from prostate cancer. Results of pooled sensitivity and specificity were 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.[27] 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.[28] 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.

3.3. Targeting PSMA for Prostate Cancer Detection

Prostate-specific membrane antigen (PSMA), also known as folate hydrolase I (FOLH1) 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 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.[29,30] 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.[31,32,33] In addition to high expression in malignant prostatic tissue and being directly related to tumor aggressiveness,[34] PSMA has also been detected in renal proximal tubules, in cells of the intestinal brush border membrane, in rare cells in the colonic crypts, in brain, salivary glands,[23,31,35,36] and in the neovasculature of nonprostatic solid carcinomas (e.g., renal cell, breast, colon, pancreas, melanoma, and lung carcinoma).[21]

A radiolabeled anti-PSMA monoclonal antibody (mAb) 7E11, marketed as Indium 111 ProstaScint® (capromab pendetide) is currently being 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. Furthermore, ProstaScint targets the intracellular domain of PSMA and is therefore thought to bind mostly necrotic portions of the prostate tumor.[32]

More recently, 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.[30] Early promising results in man from various phase 1 and 2 trials have utilized PSMA as a therapeutic target.[37,38] 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 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 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 SPECT agent, ^{99m}Tc-MIP-1404, is currently in phase 3 testing for the detection of clinically significant prostate cancer in patients with low grade disease.[39,40] 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 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, positive and predictive values for lymph nodes were 100%, 100% and 69%, respectively.[41] 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%).[42] Studies have also been conducted to compare ^{68}Ga-PSMA PET/CT and ^{18}F-choline PET/CT 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.[43] In patients with biochemical recurrence of prostate cancer with a negative [^{18}F]-choline PET/CT, ^{68}Ga-PSMA-PET/CT identified sites of recurrent disease in 43.8% of the patients with negative F-choline PET/CT scans.[44] Another study was conducted to compare the detection rate of two PSMA-targeted PET/CT imaging agents side-by-side (^{18}F-DCFPyL and ^{68}Ga-PSMA) in patients with recurrence of prostate cancer.[45] The results showed that ^{18}F-DCFPyL PET/CT provided high image quality and visualized small prostate lesions with excellent sensitivity. Furthermore, 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 Ga generators, and higher image resolution due to the intrinsic physical properties of F-18 (lower positron emission energy compared to Ga-68). Thus, overall, ^{18}F-DCFPyL PET/CT may represent a promising alternative to ^{68}Ga-PSMA PET/CT for imaging prostate cancer.

PyL is a radiolabeled PSMA-targeted small molecule discovered at JHU that was in-licensed by Progenics in 2015. It is currently being studied in phase 1 and phase 2 clinical trials under JHU's IND 121,064 for the detection of primary and metastatic prostate cancer. In collaboration with JHU, Progenics plans to complete the clinical development program of PyL and eventually seek FDA approval of PyL for the detection of prostate cancer.

3.4. ^{18}F-DCFPyL

^{18}F-DCFPyL Injection is a radiolabeled small molecule that binds to the extracellular domain of 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 1.1 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 from a 14-day single dose rat toxicology studies with DCFPyL resulted in a no observed adverse effect level (NOAEL) of 0.5 mg/kg, the highest dose tested. The maximum human mass dose of DCFPyL is expected to be 4 µg; thus, this represents an estimated safety margin of >1200-fold the human equivalent dose.

Several investigator-initiated clinical studies with ^{18}F-DCFPyL Injection in prostate cancer, as well as non-prostate cancer, are currently ongoing at Johns Hopkins University under IND 121,064. As of March 2016, ^{18}F-DCFPyL Injection has been administered to a total of 108 subjects at doses averaging 9 ± 1 mCi per injection. Preliminary safety and efficacy data from two of these studies (J1418, J1545) are currently available.

Study J1418 is a first in human, phase 1/2 study, conducted to evaluate the radiation dosimetry, biodistribution, metabolism, and safety of ^{18}F-DCFPyL Injection with PET/CT imaging in men with metastatic prostate cancer. Once safety was established, the utility of ^{18}FDCFPyL PET/CT imaging to detect local, nodal, and/or metastatic prostate cancer was assessed in men with advanced prostate cancer.

Study J1545, a phase 2 single-center, open-label study in men diagnosed with biochemical recurrence of prostate cancer. The study was conducted to evaluate the safety of ^{18}F-DCFPyL Injection, to determine the location of putative sites of metastatic disease by ^{18}F-DCFPyL PET/CT, to correlate findings on ^{18}F-DCFPyL PET/CT with conventional imaging, and to assess treatment response by ^{18}F-DCFPyL PET/CT following six months of standard of care therapy.

Data from these clinical studies at JHU demonstrate that PET imaging with ^{18}F-DCFPyL Injection is feasible and safe. Biodistribution following administration of ^{18}F-DCFPyL 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 prospectively detect residual tumor as well as regional or distance metastases with high sensitivity and specificity.

Safety results from all ongoing studies at JHU to date indicate that ^{18}F-DCFPyL Injection is well tolerated, with no reported serious adverse events in any of the studies thus far. A total of 6 adverse events have been reported, one of which was attributed as possibly related to study drug (Grade 1 Headache).

Progenics has obtained authorization from JHU to reference, and incorporate by reference, the data from the phase 1 and phase 2 studies conducted under the JHU IND. Based on the promising results from these clinical studies, Progenics plans to initiate the current phase 2/3 study (PyL 2301) under a new, separate IND to investigate the safety and efficacy of PyL imaging in patients with prostate cancer.

3.5. Rationale for Dose Selection

Prior to the first-in-human study with PyL (Study J1418) at JHU, human dosimetry was extrapolated from a preclinical biodistribution study in xenograft mice.[46] 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/g in 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 urinary bladder wall was projected to be the organ with the highest absorbed dose. To limit the radiation-absorbed dose to the urinary bladder ($\leq$ 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 $\leq$9 mCi. The 9 mCi administered dose of ^{18}F-DCFPyL Injection results in a comparable radiation dose to that of other radiotracers used in oncology such as [^{18}F]-FDG.

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Primary Objective

The primary objective of the study is to assess the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to determine the presence or absence of metastatic disease in pre-prostatectomy patients with high risk prostate cancer (cohort A)

4.2. Secondary Objectives

1. To evaluate the safety and tolerability of ^{18}F-DCFPyL
2. To assess the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to determine the presence or absence of prostate cancer within sites of metastasis or local recurrence (cohort B)
3. To determine detection rates of ^{18}F-DCFPyL PET/CT and conventional imaging among lesion locations (e.g., bone, lymph nodes, soft tissue, prostate gland)
4. To determine positive and negative predictive value (PPV and NPV) of ^{18}F-DCFPyL PET/CT imaging
5. To determine the pharmacokinetics, biodistribution, and excretion of ^{18}F-DCFPyL

4.3. Exploratory Objectives

1. To assess ^{18}F-DCFPyL uptake among lesion locations (e.g., bone, lymph nodes, soft tissue, prostate gland)
2. To assess the relationship between ^{18}F-DCFPyL uptake in prostatic and extraprostatic lesions with baseline PSA and testosterone levels, and Gleason Score at time of radical prostatectomy
3. To assess the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to detect prostate cancer within the prostate gland (cohort A)
4. To assess the impact of ^{18}F-DCFPyL PET/CT imaging on clinical management plans
5. To determine the PPV of ^{18}F-DCFPyL PET/CT imaging for lesions detected by PET that are outside the planned surgical template or biopsy site

5. TRIAL ENDPOINTS

5.1. Primary Endpoints

1. Specificity of ^{18}F-DCFPyL PET/CT imaging to determine the absence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology (cohort A)
2. Sensitivity of ^{18}F-DCFPyL PET/CT imaging to determine the presence of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology (cohort A)

5.2. Secondary Endpoints

1. Safety and tolerability (Cohorts A and B combined):
   a. Treatment-emergent adverse events
   b. Pre- and post-^{18}F-DCFPyL PET/CT lab values, ECGs and vital signs
2. Sensitivity of ^{18}F-DCFPyL PET/CT imaging to detect prostate cancer within sites of metastasis or local recurrence relative to histopathology (Cohorts B)
3. Comparison of detection rates (Cohorts A and B combined) for lesion counts overall and by location (i.e., bone, lymph nodes, soft tissue, prostate gland) between ^{18}F-DCFPyL and conventional imaging
4. PPV and NPV of ^{18}F-DCFPyL PET/CT imaging (Cohort A) to predict prostate cancer within the prostate gland and lymph nodes
5. PPV of ^{18}F-DCFPyL PET/CT imaging to predict prostate cancer within sites of local recurrence and other metastatic lesions (cohort B)
6. Pharmacokinetic parameters [e.g., C_{max}, area under the curve (AUC), total clearance (CL), steady-state volume of distribution (V_{ss}) and mean residence time (MRT)] (subset of Cohorts A and B combined)

5.3. Exploratory Endpoints

1. ^{18}F-DCFPyL uptake in different lesion locations (i.e., bone, lymph nodes, soft tissue, prostate gland) as defined by SUV_{peak}, SUV_{max}, SUV_r results derived from central readers, compared to histopathology (cohorts A and B)
2. To assess the relationship between SUV_{peak}, SUV_{max} and SUVr in prostatic and extraprostatic lesions with each of the following: baseline PSA, baseline testosterone level, and Gleason Score at time of radical prostatectomy
3. Sensitivity and specificity of ^{18}F-DCFPyL PET/CT imaging to detect prostate cancer within the prostate gland relative to histopathology (cohort A)
4. Changes to clinical management plan based on a review of clinical and radiographic subject data before and after ^{18}F-DCFPyL PET/CT imaging by a central panel of disease experts using a structured questionnaire

5. PPV of ^{18}F-DCFPyL PET/CT imaging in subjects with corresponding histopathology that is outside the planned protocol surgical template or biopsy site

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an open-label, non-randomized, Phase 2/3, multi-center 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).

Eligible subjects (see Section 7.1 for Inclusion Criteria) will be enrolled in a non-randomized, sequential manner, with competitive enrollment between study sites.

Diagnostic performance characteristics of ^{18}F-DCFPyL PET/CT imaging will be evaluated using histopathology as the truth standard. See Section 8.4 for details on blinding.

The study will explore changes to clinical management plans based on data before and after ^{18}F-DCFPyL PET/CT imaging.

This study is planned to be performed in approximately 10 sites in the United States and Canada.

See Figure 1 and Table 3 for the study schema and schedule of assessments.

6.2. Number of Subjects

Approximately 377 subjects are planned to be dosed in this study:

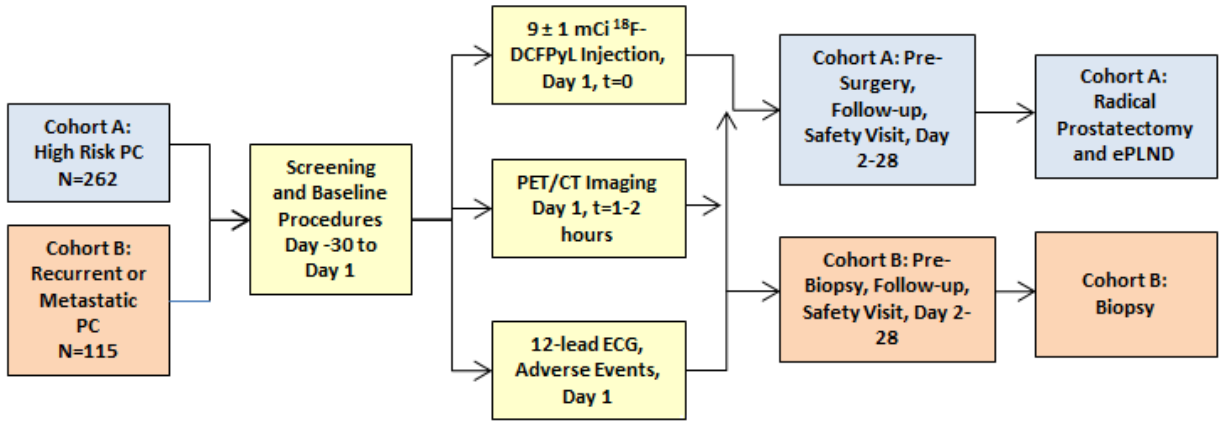
- Approximately 262 subjects will be dosed in Cohort A.
- Approximately 115 subjects will be dosed in Cohort B.

See Section 7 for complete eligibility details and Section 12.1 for complete sample size assumptions.

6.3. Treatment Assignment

All subjects will be administered 9 ± 1 mCi (333 ± 37 MBq) ^{18}F-DCFPyL Injection followed by PET/CT imaging as illustrated in the schema below. See Section 9.6 Study Drug Administration and Table 3 Schedule of Assessments for complete details.

Figure 1: Study Schema



6.4. Dose Adjustment Criteria

Dosing adjustments of ^{18}F-DCFPyL Injection are not permitted.

6.5. Study Duration

The duration of subject participation will be from informed consent through ^{18}F-DCFPyL PET/CT scanning and follow-up visit, a total maximum duration of 58 days.

6.6. Safety Monitoring

An independent Data Monitoring Committee (DMC) will not be used for this open label study. However, safety monitoring will consist of continuously monitoring adverse events on an ongoing basis in accordance with Section 11. A Safety Review Committee, consisting of Sponsor representatives (e.g., Medical Monitor, Clinical Operations designee, Biometrics designee) and at least one active Principal Investigator will also review data on an ongoing basis to assess subject safety, eligibility and baseline characteristics through listings, tables and subject profiles.

6.7. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at any time. In the event of serious, unexpected and related adverse events, the program may be stopped prematurely upon advice from the Safety Review Committee, the Sponsor or upon request from the FDA. In addition, the Sponsor or the Institutional Review Board (IRB) or Ethics Committee (EC) may terminate an investigational site for the following (but not limited to) reasons:

- If any safety issues occur;
- Failure of the Investigator to comply with pertinent International Conference on Harmonisation (ICH) E6 guidelines on Good Clinical Practice (GCP) guidelines and regulations;
- If serious protocol violations occur;

- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or other party involved in the study;
- Failure of the Investigator to enroll subjects into the study at an acceptable rate as agreed-upon with the Sponsor

Table 3: Schedule of Assessments

	Screening / Baseline	**^{18}F-DCFPyL Dosing**	**^{18}F-DCFPyL Imaging**	**Pre-Surgery/Biopsy Follow-Up**
	Day-30 to Day 1	**Day 1**	**1-2 Hours Post Dosing**	**Within 28 Days Post Dosing**
Cohorts A and B				
Informed Consent & Eligibility	X			
Demographics (date of birth, race, ethnicity, height, weight, BMI)	X			
Medical History (see Section 11.1.1)	X			
Prior Cancer Medications & Treatments	X			
Clinical Labs (Hematology, Chemistry) see Table 6	X[1]			X
PSA (Total) & Testosterone	X[1]			
Vital Signs (Blood Pressure, Heart Rate, Temperature, Respiratory Rate)	X	X (pre-dosing)	X (pre-imaging)	X
12-Lead Electrocardiogram (ECG) (see Section 11.1.4)		X (pre-dosing)	X (pre-imaging)	
^{18}F-DCFPyL Administration (see Section 9)		X		
Whole Body PET/CT (see Section 10.1)			X	
Adverse Events (see Section 11.2.1.1)		X		X[5]
Concomitant Medications (see Section 8.2)	X	X		X
Conventional Imaging (CT or MRI, Bone Scan) (see Section 10.1)	X[2]			
Surgery or Image-Guided Biopsy				X[3,6]

Table 3: Schedule of Assessments

	Screening / Baseline	^{18}F-DCFPyL Dosing	^{18}F-DCFPyL Imaging	Pre-Surgery/Biopsy Follow-Up
	Day-30 to Day 1	Day 1	1-2 Hours Post Dosing	Within 28 Days Post Dosing
Subset of Cohort A or B at Johns Hopkins University only for Pharmacokinetic (PK) Analysis				
Blood Collection		X (9 collections)[4]		
Urine Collection		X (3 collections)[4]		
Whole Body PET/CT			X (3 scans)[4]	

[1] To be collected prior to dosing, if collected on day of dosing. If PSA and testosterone have not been tested within 30 days of study drug injection, a blood draw will be collected prior to dosing.
[2] If not obtained as standard of care ≤ 6 weeks (Cohort A) or ≤ 4 weeks (Cohort B) prior to Day 1. Na-^{18}F-PET bone scans conducted at screening must be at least 10 hours prior to dosing (see Section 7.2).
[3] Surgery or biopsy to occur at least 12 hours from time of ^{18}F-DCFPyL dosing but not more than 28 days from dosing. In Cohort B, imaging used to guide biopsy (i.e., CT, MRI) will be submitted to a central core imaging lab.
[4] See Section 10.6 for complete details. Analysis should occur immediately following last sample collected.
[5] A safety phone call will also occur 7(±3) days post-dosing [if surgery (Cohort A) or biopsy (Cohort B) has not yet occurred] and 21(±7) days post biopsy (Cohort B). See Section 11.2.1.1 for complete details.
[6] If a subject's planned procedure (RP or biopsy) for prostate cancer changes following ^{18}F-DCFPyL imaging, the alternate or additional prostate cancer procedure and corresponding histopathology data will be recorded in the electronic case report form (eCRF).

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

All Cohorts:

1. Adults ≥18 years of age.
2. Subjects provide signed informed consent and confirm that they are able and willing to comply with all protocol requirements.
3. Histologically confirmed adenocarcinoma of the prostate.

Cohort A Only:

4. At least high risk prostate cancer defined by NCCN Guidelines Version 3.2016 (clinical stage ≥T3a or PSA >20 ng/mL or Gleason score ≥8).[47]
5. Scheduled or will be scheduled to undergo radical prostatectomy with PLND.

Cohort B Only:

6. Radiologic evidence of local recurrence or new or progressive metastatic disease demonstrated on anatomical imaging (CT, MRI, or ultrasound), whole-body bone scan (^{99m}Tc-MDP or Na^{18}F) within 4 weeks of Day 1.
7. If prior treatment with radiation or ablative therapy, evidence of recurrence outside the confines of prior treated site(s).
8. Scheduled or will be scheduled for percutaneous biopsy of at least one amenable lesion.

7.2. Subject Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for this study:

All Cohorts:

9. Subjects administered any high energy (>300 KeV) gamma-emitting radioisotope within five physical half-lives, or any IV iodinated contrast medium within 24 hours, or any high density oral contrast medium (oral water contrast is acceptable) within 5 days, prior to study drug injection.
10. Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise obtaining reliable data, achieving study objectives, or completion.

Cohort A Only:

11. Patients with prior androgen deprivation therapy or any investigational neoadjuvant agent or intervention

Cohort B Only:

12. Prior radiation or ablative therapy to intended site of biopsy, if within the prostate bed.
13. Initiation of new systemic therapy for recurrent and/or progressive metastatic disease since radiographic documentation of recurrence/progression.

7.3. Subject Withdrawal Criteria

A patient may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw patients from the study. Subjects may be discontinued for any of the following reasons:

- Significant protocol violation or noncompliance (e.g., initiation of treatments forbidden per Section 7.2)
- Adverse event that precludes further study participation
- Best medical interest of the patient (Investigator decision)
- Sponsor terminates the study
- Subject requests to be withdrawn from the study
- Subject is lost to follow-up
- Death

Should a subject withdraw, all efforts will be made to complete the required study procedures as thoroughly as possible.

Data will be collected for all withdrawn subjects up until the time of discontinuation. The reason for discontinuation from the study will be recorded in the subject's eCRF.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

A single administration of ^{18}F-DCFPyL Injection (PyL) will be administered 1-2 hours prior to PET/CT imaging on Day 1.

Table 4: Investigational Product

	Investigational Product
Product Name	^{18}F-DCFPyL INJECTION (PyL)
Dosage Form	Sterile solution for intravenous injection
Unit Dose	9 ± 1 mCi (333 ± 37 MBq)
Route of Administration	Intravenous catheter placed in an antecubital vein or an equivalent venous access
Physical Description	Colorless, particle-free solution

8.2. Concomitant Medications and Procedures

All concomitant medications and medical procedures that occur within 7 days of consent will be recorded.

Any new prostate cancer therapy is ***strictly prohibited*** from time of dosing (Day 1) to surgery (Cohort A), or from time of radiographic documentation of disease progression to biopsy (Cohort B). If a subject reports having received a new prostate cancer therapy (e.g., hormone, drug, biologic, radiologic, or chemotherapy) or alternate medical procedure(s) for prostate cancer, during these time periods, the subject should be discontinued from the study.

Medical procedure(s) and histopathology data for subjects who do not receive the planned protocol procedure but who received alternate or additional medical procedure(s) for prostate cancer will be recorded in the eCRF.

8.3. Treatment Compliance

All ^{18}F-DCFPyL drug injected will be administered under the supervision of the investigator, or qualified designee. Details of the study drug injection will be captured in each subject's source documents.

8.4. Randomization and Blinding

This is an open-label, non-randomized study. Three independent readers from a central imaging core lab will be given access to ^{18}F-DCFPyL PET/CT imaging, conventional imaging, and biopsy-guided imaging. The central readers will be blinded to all other clinical information and radiology assessments. Likewise, the Investigator is responsible for ensuring that local pathologists who generate the histopathology results for the primary endpoint remain blinded to all imaging results.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Please reference Section 8.1 for a description of the study drug.

9.2. Restrictions

9.2.1. Food and Fluid Intake

There are no dietary or food restrictions for this trial.

Increased fluid intake should occur before and after image acquisition to maintain proper hydration throughout the study period and decrease radiation exposure to the urinary bladder. To enhance imaging, subjects should be encouraged to void post study drug injection and prior to imaging.

Subjects should follow pre-imaging and preoperative guidelines as per institutional practices and in accordance with standard of care principles.

9.2.2. Activity

The radioactivity administered in this study is similar to other diagnostic radiopharmaceuticals and should be managed according to institutional policies.

9.3. Study Drug Packaging and Labeling

The final drug product (^{18}F-DCFPyL) is a clear, colorless injectable solution at a strength of 5-75 mCi/mL (185-2775 MBq/mL) ^{18}F-DCFPyL at End of Synthesis (EOS). ^{18}F-DCFPyL will be dispensed and filled into a unit-dose syringe. The final drug product will be placed into a lead pig and delivered to the clinical site in shipping containers with lead shielding.

Labels will be generated according to local policies and meet minimum requirements for labeling radioactive materials in compliance with federal, state, and local pharmacy regulations. Progenics minimum requirements for the syringe label will include the following: subject identifier, product name, dispensing lot number, ordered dose, dispense date/time, dispensed activity and volume, and beyond use date (BUD). An auxiliary sticker reading "New Drug—Limited by Federal Law to Investigational Use" shall be affixed to the unit-dose container.

9.4. Study Drug Storage

The study drug should be maintained at room temperature within the received lead shield unit-dose system until time of administration.

9.5. Study Drug Preparation

The final drug product is supplied to each institution on the day of administration in a unit-dose syringe with no additional preparation required. Institutional policies and standard operating procedures (SOPs) should be followed for receipt and appropriate radiation safety handling. Before and after each administration, measure the amount of radioactivity in the syringe using an appropriate dose calibrator. Apply decay correction if necessary and calculate the administered dose accordingly.

9.6. Administration

Please see the Imaging Manual for complete details including pre-and post-injection measurement of the ^{18}F-DCPyL Injection dose syringe. Administration must occur by the labeled expiration time.

1. Place an intravenous catheter in an antecubital vein or an equivalent venous access.
2. Ensure patency of the line with a saline flush.
3. Inject a bolus of 9±1 mCi (333±37 MBq) of ^{18}F-DCPyL into the IV line or equivalent venous access by slow push from the appropriately shielded syringe according to normal local practices.
4. Administer an intravenous flush (e.g., 5-10 ml sterile Sodium Chloride Injection, 0.9%), to ensure full delivery of the dose.

If dose extravasation is noticed during or after completion of the drug administration:

1. Try to aspirate as much extravasated drug as possible through the still-intact catheter.
2. Imaging should proceed unless contraindicated for safety reasons.
3. Examine the skin area for local toxicity before discharge, and instruct subject to contact site immediately if local symptoms at injection site do not improve or worsen.
4. Note the event as an Adverse Event in the CRF and notify the Sponsor within 24 hours.

9.7. Study Drug Accountability

In accordance with ICH and FDA requirements, the investigator and/or drug dispenser must at all times account for all study drug furnished to the institution and prepared for the patient, whether used or unused.

No study agent is to be used outside of this study. Accurate and adequate accountability records must be maintained by the radiopharmacy, hot lab or nuclear medicine department responsible for receipt and dispensation of study drug. Records should include at minimum:

- Dates of receipt, lot number and quantities received from Sponsor or designee;
- Dates, subject numbers, and amount dispensed for administration to specific subjects;
- If applicable, dates, lot numbers, and drug quantities destroyed.

The investigator is responsible for ensuring that study agents are administered only to subjects included in this study in accordance with the study protocol.

Throughout the study, drug accountability will be performed by appropriate Sponsor personnel and when appropriate, reconciliation will be performed.

9.8. Study Drug Handling and Disposal

^{18}F-DCFPyL Injection is a radioactive drug and should be handled by personnel trained in the proper use and disposal of radiopharmaceuticals according to institutional policies and applicable regulations or guidance. When handling and administering ^{18}F-DCFPyL Injection, follow aseptic procedures and use effective radiation shielding, and appropriate safety measures to minimize radiation exposure.

Empty or unused product should be decayed at the site according to institutional policies and applicable state and federal regulations. Record the use and/or decay of study agent on the Drug Accountability record.

10. ASSESSMENT OF EFFICACY

10.1. Image Acquisition

10.1.1. ^{18}F-DCFPyL PET/CT (all cohorts)

^{18}F-DCFPyL PET imaging will be performed on local PET/CT scanners with CT for correction of physical effects (e.g., attenuation, scatter) and anatomic localization.

At 1-2 hours post ^{18}F-DCFPyL injection, the subject will be asked to void, and a whole body CT and PET scan will be acquired from the mid-thigh through the vertex of the skull. Parameters for PET/CT scanning can be found in the Imaging Manual.

10.1.2. Bone Scan (all cohorts)

A radionuclide bone scan (either ^{99m}Tc-MDP or ^{18}F-NaF PET/CT, depending upon the site's standard of care) will be obtained at Screening if one has not been obtained within six weeks (Cohort A) or four weeks (Cohort B) prior to study drug injection. If conducted as part of Screening, ^{18}F-NaF PET bone scans must be done at least five physical half-lives (10 hours) prior to ^{18}F-DCFPyL injection. Bone scan images will be submitted to the independent central imaging core lab per instruction in the Imaging Manual for assessment.

10.1.3. CT or MRI (all cohorts)

A contrast-enhanced CT of the chest, abdomen and pelvis (or non-contrast CT chest with Gadolinium-enhanced MRI of the abdomen and pelvis for subjects who have a medical contraindication to iodinated contrast) will be obtained at Screening if not already obtained within 6 weeks (Cohort A) or 4 weeks (Cohort B) prior to study drug injection. If CT is conducted at Screening, IV iodinated contrast medium cannot be administered within 24 hours of study drug injection. High density oral contrast medium (oral water contrast is acceptable) cannot be administered within 5 days prior to study drug injection. Copies of baseline CT or MR images will be submitted to the independent central imaging core lab per instruction in the Imaging Manual for assessment.

10.1.4. Biopsy Guided Imaging (cohort B only)

In Cohort B, imaging used to guide biopsy (i.e., CT/MRI) will be collected and reviewed centrally to confirm the biopsy location in the area of interest. The instruction for capturing biopsy images and directions for submitting the images to the independent central imaging core lab will be found in the Image Guided Biopsy Manual.

10.2. Image Interpretation

An independent imaging core lab will receive and evaluate ^{18}F-DCFPyL PET/CT baseline, conventional images, and imaging used to guide biopsy (i.e., CT, MRI). The processes for image acquisition, transmittal and interpretation are detailed in the Imaging Manual and Imaging Review Charter documents.

10.3. Prostatectomy and Lymphadenectomy

Within 28 days post-study drug injection, all subjects in Cohort A will undergo standard of care RP with PLND as detailed in the Surgical Manual. Extent of PLND will be captured in the eCRF.

Surgical staff will label all specimens removed during surgery to correlate with the specific anatomic location of removal, in accordance with the Surgical Manual.

Should a subject receive alternate or additional procedure(s) for prostate cancer after dosing, the procedure and corresponding histopathology data will be recorded in the eCRF.

10.4. Interventional Radiology

Up to two lesions (one bone and one soft-tissue lesion, wherever feasible) may be biopsied in cohort B, within 28 days following ^{18}F-DCFPyL imaging. If more than one lesion is obtained, the interventional radiologist will identify the specimen to be evaluated for diagnostic assessment and statistical analysis. The lesions most preferred for biopsy will be those that are suspicious on all or most imaging modalities and are in the investigators judgement safe for biopsy. The final biopsy site will be decided in consultation with the Interventional Radiology service for feasibility. Details regarding the collection of imaging used to guide biopsy (e.g., X-ray, CT, MRI) and transmittal to the central imaging lab can be found in the Image Guided Biopsy Manual. Images will be reviewed centrally to confirm uptake of ^{18}F-DCFPyL in the area of interest.

Should a subject receive alternate or additional procedure(s) for prostate cancer after dosing, the procedure and corresponding histopathology data will be recorded in the eCRF.

10.5. Biopsy and Surgical Pathology

Immediately following biopsy or surgery, the specimens will be sent for histopathological processing and analysis at the site in accordance with the study Pathology Manual.

Gross handling of the prostate gland and lymphadenectomy specimens, if applicable, will include whole gland assessment and sectioning of the entire prostate gland, overall measurement of specimen size, lesion location, dissection and description (including location) of identified lymph nodes, and submission of lymph nodes in their entirety plus all remaining fibroadipose tissue for each harvested regional packet. Histopathology results of the prostate gland and pelvic lymph nodes (Cohort A) or biopsy location (Cohort B) will be recorded in the eCRF.

Should a Cohort A subject forego RP surgery and undergo alternative procedure for prostate cancer (e.g., biopsy), the procedure and corresponding histopathology data will be recorded in the eCRF. Likewise, should a Cohort B subject receive additional procedure for prostate cancer, the procedure and corresponding histopathology data will be recorded in the eCRF.

10.6. Pharmacokinetics

A total of 10 subjects from either cohort at the JHU site will complete the pharmacokinetics (PK) portion of the study. For detailed instructions on sample collection, processing, and analysis, please refer to the PK Manual.

A 4.5 mL blood sample will be collected at the following nine time points: pre-dose, 5±2 m, 15±2 m, 30±5 m, 1±0.25 hr, 2±0.25 hr, 4±0.25 hr, 6±0.25 hr, and 8±0.25 hr post-dose.

Urine samples will be collected over the following intervals: 0-2 hr, 2-4 hr and 4-8 hr post dose.

Whole body PET/CT scans will be collected at three time points: up to 17 minutes after PyL injection and prior to voiding, 1± 0.25 hr and 4± 0.25 hr post dose.

Table 5: PK Sampling & Imaging Timepoints

Procedure	**Pre-dose**	**0 hr**	**5±2 m**	**15± 2 m**	**30± 5 m**	**1± 0.25 hr**	**2± 0.25 hr**	**3± 0.25 hr**	**4± 0.25 hr**	**6± 0.25 hr**	**8± 0.25 hr**
^{18}F-DCFPyL Administration		X									
Blood & Plasma Collection	X		X	X	X	X	X		X	X	X
Urine Collection		<----------X---------->					<-----X----->		<------X------>		
^{18}F-DCFPyL PET/CT Imaging		X				X			X		

Analysis will be generated as described below and in Section 12.5.4. Aliquots of blood, plasma and urine samples will be batch counted in an automated gamma counter immediately following the sample collection period. Resulting raw radioactivity counts will be converted into radioactivity concentrations using an aliquot of the dosing formulation as a reference standard.

Blood concentration-time data will be computed by non-compartmental analysis and pharmacokinetic parameters, e.g., C_{max}, AUC, CL, V_{ss}, and MRT will be generated. Ratios of blood to plasma radioactivity at each time point will be calculated.

The total amount of excreted radioactivity per urine collection interval will be calculated as a product of urine radioactivity concentration and volume, and then expressed as a percent of administered dose.

Metabolic profiles in urine will be determined using radio-chromatographic methods. The areas under the radio-chromatographic peaks corresponding to the parent compounds and putative metabolites, if applicable, will be used in the qualitative assessment of metabolic profiles in urine.

Whole-body PET/CT images acquired immediately after PyL injection and at 1 hr and 4 hr post-dose will be used to obtain volumes and activity concentrations for selected tissues/organs. Based on these data, time-integrated activity coefficients will be derived and may be used for subsequent calculation of radiation absorbed doses using the OLINDA/EXM software. This analysis will be described in a dosimetry report for ^{18}F-DCFPyL.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Demographic and baseline information, including date of birth, race, and ethnicity, will be collected.

A complete prostate medical history will be obtained at the first screening visit. Prostate medical history includes review of prostate disease history, prostate cancer staging, PSA results, biopsy results, and all past/present therapies.

Other clinically relevant medical history will be collected prior to study drug administration. This should include any past and/or current medical conditions that, in the opinion of the investigator, are clinically relevant regardless of whether it has resolved. Special attention should be paid to prior malignancies other than prostate cancer or concurrent or past conditions that can change pelvic anatomy or cause lymphadenopathies (e.g., viral, bacterial or parasitic infections).

11.1.2. Vital Signs

Vital sign measurements will include temperature, respiratory rate, blood pressure, and heart rate. All measurements should be obtained from the subject in the sitting position and measured at two intervals on the day of dosing, including pre-dosing and pre-imaging.

11.1.3. Weight and Height

Height, weight, and BMI at screening will be captured.

11.1.4. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be taken at two intervals on the day of dosing, including prior to dosing and prior to imaging. Please refer to the ECG Procedure Manual for acquisition and transmittal details. The onsite Investigator has the responsibility to evaluate the ECG for the assessment of subject safety. Adverse events will be reported in the CRF.

11.1.5. Laboratory Assessments

11.1.5.1. Hematology, Blood Chemistry, PSA and Testosterone

A blood draw will be collected at the screening and follow-up visits as stated in Table 6. Clinical hematology and blood chemistry will be evaluated for safety monitoring. If PSA and testosterone have not been tested within 30 days of study drug injection, a blood draw will be collected prior to dosing.

Table 6: Clinical Laboratory Tests

Category	Analytes	Frequency[1]
Hematology	CBC: *WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), WBC count, RBC count, Hematocrit, Hemoglobin, Platelets*	Screening, Follow-Up
Chemistry	CMP: *Sodium, Potassium, Calcium, Chloride, Glucose, BUN, Creatinine, Total Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin, Total Protein*	Screening, Follow-Up
PSA	Total	Screening
Testosterone	Total	Screening

CBC=complete blood count; WBC=white blood cell; RBC=red blood cell; CMP=comprehensive metabolic panel; BUN=blood urea nitrogen; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PSA=prostate-specific antigen

[1] Blood draws and laboratory testing will be conducted according to local standard practices. PSA and testosterone resulted within 30 days of Day 1 does not need to be re-tested.

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical occurrence or the deterioration of a pre-existing condition following or during exposure to a pharmaceutical product, whether or not considered related to the product.

All AEs (related and unrelated) will be collected on the day of, after ^{18}F-DCFPyL dosing and at time of follow-up visit (pre-surgery/biopsy). Adverse events will also be assessed via a safety phone call at the following timepoints, if applicable: 1) 7 (±3) days post study drug injection (if surgery or biopsy has not yet occurred), and 2) 21 (±7) days post biopsy.

All AEs, whether or not they are related to study drug, must be recorded on the study case report forms.

11.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity

- Results in a congenital abnormality or birth defect of a subject's child
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any patient/subject has been dosed until study completion, whether or not related to the study, must be recorded on forms provided by the Sponsor, or designee.

11.3. Relationship to Study Drug

The Principal Investigator or Sub-Investigator must make the determination of relationship to the investigational product for each AE (Unrelated or Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

11.4. Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site.

The investigator should assess all clinical laboratory results for clinical significance and record the assessment in source documents. The investigator should evaluate any laboratory result change from pre- and post-study drug administration to determine if the change meets the definition of an AE or SAE. Record any clinically significant lab results determined to meet the definition of an AE and SAE on the AE eCRF and SAE Report Form, respectively.

Information about AEs and SAEs will be collected from the first administration of study drug until the pre-surgery/biopsy follow-up visit. The AE term should be reported in standard medical terminology and be the medical diagnosis when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the NCI CTCAE, version 4.03. If the CTCAE grading is not defined in the NCI CTCAE grading table for a particular AE, severity will be rated according to the following definitions

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)
- Life Threatening (immediate risk of death from the event as it occurred)
- Death (death related to adverse event)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded at the same interval defined for AE collection as indicated in Section 11.2.1.1 . Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Progenics or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email or fax to Sponsor, or designee.

Additional follow-up information, if required or available, should promptly be emailed or faxed to Sponsor, or designee via a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Progenics Pharmaceuticals, Inc. is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12. STATISTICS

12.1. Sample Size

Approximately 262 subjects will be dosed in cohort A. No formal power calculations will be performed for cohort B; reliable estimates should be achievable from approximately 115 dosed. This results in a total sample size of approximately 377 subjects dosed in the study.

The primary analysis in Cohort A will test the co-primary endpoints of sensitivity and specificity of ^{18}F-DCFPyL PET imaging relative to histopathology for metastatic disease in pre-prostatectomy patients. For each co-primary endpoint there will be three independent imaging readers. At least two of the three readers must reject the null hypothesis for specificity to be deemed a success. If specificity is a success, then the same two readers need to reject the null

hypothesis for sensitivity to reach overall success of the primary endpoint. The null hypotheses will be tested in the following order:

1. Specificity of ^{18}F-DCFPyL PET/CT imaging relative to histopathology in cohort A

   H_0: $\pi_{Sp} = 0.80$ versus H_1: $\pi_{Sp} \neq 0.80$,
2. Sensitivity of ^{18}F-DCFPyL PET/CT imaging relative to histopathology in cohort A

   H_0: $\pi_{Se} = 0.40$ versus H_1: $\pi_{Se} \neq 0.40$

where π_{Se} is the true sensitivity and π_{Sp} is the true specificity of ^{18}F-DCFPyL PET imaging.

A total of approximately 262 subjects from Cohort A will provide 80% power to reject the null hypothesis about sensitivity at the 5% significance level if the true sensitivity is at least 60% and at least 80% power to reject the null hypothesis about specificity at the 5% significance level if the true specificity is at least 87.8%. These calculations are based on the following assumptions:

- the probability of a positive histopathology sample in Cohort A is 20%,

The sample size is based on the normal approximation to the binomial distribution without a continuity correction[48]:

$$n \geq \left\{ \frac{z_{\alpha/2}\sqrt{P_0(1-P_0)} + z_{\beta}\sqrt{P_1(1-P_1)}}{P_1 - P_0} \right\}^2$$

P_0 are P_1 are values of sensitivity under the null and alternative hypotheses, respectively. After adjusting sensitivity and specificity separately by their corresponding prevalence values, a total in 236 evaluable subjects are needed in cohort A. Assuming 10% drop out or non-evaluable rate increases the required number of subjects in cohort A to approximately 262.

The type I error rate of 5% will be preserved by requiring that both null hypotheses be rejected in order to draw the conclusion that ^{18}F-DCFPyL is efficacious for imaging. The second primary endpoint is only tested if the first primary endpoint is rejected at 5% per a fixed sequential method. If the first hypothesis fails to be rejected, no further testing will be conducted.

12.2. Analysis Populations

12.2.1. Screened Subjects

All subjects who sign an informed consent document will be included in the *screened subject* population.

12.2.2. Safety Set

All subjects who receive any amount of ^{18}F-DCFPyL will be included in the *safety set.*

12.2.3. Evaluable Set

Evaluable subjects in Cohort A are those who provide a ^{18}F-DCFPyL PET image result (positive or negative) and a corresponding RP histopathology result (positive or negative).

Evaluable subjects in Cohort B are those who provide a ^{18}F-DCFPyL PET image result (positive or negative) and a corresponding biopsy histopathology result (positive or negative for each

subject), along with a conventional image that confirms the location of the histopathology sample.

12.2.4. Per Protocol Set

The *per protocol* set is the evaluable set, excluding subjects with major protocol deviations impacting efficacy endpoint(s).

12.2.5. PK Evaluable Set

Subjects who provide at least six of the nine scheduled blood samples will be evaluable for PK analysis of blood samples. Subjects with at least two of the three scheduled urines will be evaluable for PK analysis of urine samples.

12.3. Endpoints and Derivations

12.3.1. Sensitivity, Specificity, PPV, and NPV

Table 7 will be used to classify the combined pelvic lymph node packets (left or right) from Cohort A and biopsy from Cohort B according to its ^{18}F-DCFPyL image result (positive or negative) generated from central imaging review and its histopathology result (positive or negative for prostate cancer) generated by the sites' pathology review. Nodes identified on ^{18}F-DCFPyL PET/CT images in areas that were not removed in surgery for Cohort A will not be tabulated due to absence of histopathology.

Table 7: Classification of ^{18}F-DCFPyL Imaging Result and Histopathology Result for Cohorts A and B Separately

	Histopathology Result		
^{18}F-DCFPyL Image	**Positive***	**Negative**	
Positive	TP	FP	I(p)
Negative	FN	TN	I(n)
	R(p)	R(n)	N_1

TP=true positive; FP=false positive; FN=false negative; TN=true negative.
R(p) and R(n) denote the subjects with a positive or negative lobe or biopsy, respectively, based on histopathology.
I(p) and I(n) denote the subjects with a positive and negative lesion, respectively, based on the ^{18}F-DCFPyL image.
N_1 indicates the number of subjects with evaluable pelvic lymph node packets from Cohort A or the number of subjects with evaluable biopsies from Cohort B.
*Positive histopathology should be for prostate cancer only.

The following statistics will be computed:

- Sensitivity = TP/R(p),
- Specificity = TN/R(n),
- Positive predictive value (PPV) = TP/I(p),
- Negative predictive value (NPV) = TN/I(n).

For Cohort A, a true positive or true negative must be determined from imaging and histopathology aligning on outcome overall.

12.3.2. Lesions Per Subject

The number of lesions detected on the ^{18}F-DCFPyL PET/CT image in each of bone, lymph nodes, soft tissue, and prostate gland will be determined by each of the three central imaging core lab independent readers. The number of lesions per subject per region will be computed for each subject based on each reader's lesion count.

12.3.3. Change from Baseline

For laboratory data, baseline will be the screening/baseline value. Change from baseline will be computed as the pre-surgery/biopsy follow-up value minus the baseline value +1.

For ECG data, baseline will be the pre-dose value. Change from baseline will be computed as the post-dose value minus the pre-dose value +1.

For vital signs, baseline will be the pre-dose value. Change from baseline will be computed as the post-dose value minus the pre-dose value +1 and the pre-surgery/biopsy value minus the baseline value +1.

12.3.4. Pre-Treatment and Concomitant Medications

Pre-treatment medications are those administered prior to ^{18}F-DCFPyL administration; concomitant medications are those administered from ^{18}F-DCFPyL administration through last study visit.

12.3.5. Treatment-Emergent Adverse Events

Treatment-emergent adverse events will be those observed from the day of ^{18}F-DCFPyL administration until 7 (±3) days post study drug injection [if surgery (Cohort A) or biopsy (Cohort B) has not yet occurred] and 21 (±7) days post biopsy in Cohort B.

12.4. Missing Data

No imputation of missing data will be applied.

12.5. Analyses

In general, continuous endpoints will be summarized by visit using summary statistics: sample size, mean, standard deviation, median, minimum, and maximum. Categorical endpoints will be summarized by visit using frequencies and percentages.

12.5.1. Subject Characteristics

A disposition table will be presented to show how many subjects were screened, the number and percentage of subjects in each population set, study completers, and early discontinuations along with reasons for discontinuation.

Baseline characteristics (age in years, categorical age [<65 years, ≥65 years], race, gender, ethnicity, height [cm], weight [kg], BMI [kg/m^2]) will be summarized for all analysis population

sets. Medical history verbatim terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Subject frequencies and percentages will be tabulated by system organ class (SOC) and preferred term (PT) for all analysis population sets. Prior prostate cancer medical history will be summarized for all analysis populations. Type of CT, MRI or bone scans will be summarized along with days each occurred prior to study drug administration by all analysis populations.

Medications will be coded using the WHO Drug Dictionary. Pre-treatment medications will each be summarized by ATC4 class and generic name for all analysis population sets.

12.5.2. Efficacy Analysis

12.5.2.1. Primary Endpoint

Cohort A

The primary analysis in Cohort A will be addressed by computing point estimates and 95% two-sided confidence intervals (CIs) for specificity first and if the null hypothesis is rejected for specificity then sensitivity will be tested next. Both outcomes are on the subject level (one overall outcome per subject) in the evaluable set. If the *per protocol* population exists then this analysis will be performed on the *per protocol* population as a supplemental analysis. The normal approximation to the binomial distribution will be used. Sensitivity and specificity will be computed for each of three central imaging core lab independent readers.

The null hypothesis for specificity will be rejected if the lower limit of the 95% CI exceeds 0.80 for at least two readers. If statistical significance is achieved for specificity where the null hypothesis is rejected, then sensitivity will be tested where the null hypothesis will be rejected if the lower limit of 95% CI exceeds 0.40 for the same two readers who rejected the null hypothesis for specificity.

A sensitivity analysis will be performed to allow any 2 of the 3 central readers to reject the null hypothesis for sensitivity only after specificity has been deemed a success. This analysis will not require the same 2 central readers to reject the null hypothesis for specificity and sensitivity. This analysis will be performed for the evaluable and per protocol populations.

12.5.2.2. Secondary Endpoints

The following secondary efficacy endpoint analyses will be generated on the *evaluable set*.

Point estimates and two-sided 95% CIs will be presented for the following secondary endpoints:

- PPV and NPV will be computed for the pelvic lymph node packets (one observation per subject for cohort A).
- Sensitivity of ^{18}F-DCFPyL PET/CT imaging within sites of metastasis or local recurrence relative to histopathology (cohort B)
- PPV will be computed for the biopsies (one observation per subject for cohort B).

The normal approximation to the binomial distribution will be used for endpoints having one observation per subject. The null hypothesis will be rejected for each if the lower limit of the

95% CI exceeds 0.50 for at least 2 of the 3 central readers. Statistics will be computed for each of the three central imaging core lab independent readers.

Lesions per subject, as detected by ^{18}F-DCFPyL PET/CT and conventional images will be summarized for each tissue type (bone, lymph nodes, soft tissue, and prostate gland) and each of the three central imaging core lab independent readers using evaluable subjects from both cohorts.

12.5.2.3. Exploratory Analyses

Analyses will be generated on the *evaluable set* for the following exploratory endpoints:

- The number of lesions per subject will be plotted against baseline PSA and baseline testosterone for each of the three central imaging core lab independent readers using evaluable subjects from both cohorts.
- SUV_{max}, SUV_{peak} and SUVr will be summarized for each tissue type (e.g., bone, lymph nodes, soft tissue, and prostate gland) and each of the three central imaging core lab independent readers using evaluable subjects from both cohorts. The relationship between SUVr in prostatic lesions and baseline PSA and testosterone levels, and Gleason score at time of radical prostatectomy will be evaluated.
- Sensitivity, SUV_{max}, SUV_{peak}, and SUV_r will be computed for the following subgroups in Cohort A:
  - Previous radiation therapy (yes/no)
  - Previous hormonal therapy (yes/no)
  - Previous chemotherapy (yes/no)
- SUV_{max}, SUV_{peak}, and SUV_r will be summarized with positive and negative histopathology. Each will be summarized by Gleason score for the single or dominant prostate tumor nodule.
- The clinical management plans before and after review of ^{18}F-DCFPyL PET/CT scans will be summarized.

An exploratory analysis of PPV of ^{18}F-DCFPyL PET/CT imaging in subjects who are excluded from the *evaluable set* but have corresponding histopathology outside the planned protocol procedure will be performed on the *safety set*.

12.5.3. Safety

All safety parameters will be presented for the *safety set*.

12.5.3.1. Exposure

Volume administered (mL) and activity administered (mCi) will be summarized using the Safety Set and the Evaluable Set.

12.5.3.2. Adverse Events

Adverse event verbatim terms will be coded using MedDRA. The frequency and percentage of subjects with an adverse event and the number of events will be summarized by SOC and PT. Adverse events will also be summarized by severity and, separately, by relationship to treatment. Serious adverse events, adverse events leading to study discontinuation and adverse events leading to death will be listed.

12.5.3.3. Clinical Laboratory

Observed values and changes will be tabulated using summary statistics in the *safety set*.

12.5.3.4. ECG

Observed values and changes will be tabulated for each visit using summary statistics. Shift tables comparing pre- to post-dosing categorical ECG values will be presented using the *safety set*.

12.5.3.5. Vital Signs

Observed values and changes will be tabulated using summary statistics in the *safety set*.

12.5.4. Pharmacokinetics

Mean (±SD) and individual activity-time plots will be presented for blood (mCi/mL), urine (% injected dose excreted per collection interval) and selected organs/tissues, including "whole body" (% injected dose at each scanning time-point). Summary statistics (sample size [N], arithmetic mean, geometric mean, median, SD, minimum, and maximum) will be presented by timepoint for each of blood, urine and selected organs/tissues, including "whole body".

Summary statistics will be presented for C_{max}, area under the curve (AUC), total clearance (CL), steady-state volume of distribution (V_{ss}), and mean residence time (MRT) for the subset of subjects (PK evaluable set).

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Data collected during this study may be used to support the development, registration or marketing of ^{18}F-DCFPyL. All data collected during the study will be controlled by Progenics or designee and Progenics will abide by all relevant data protection laws.

The investigator will grant monitor(s) and auditor(s) from Progenics or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data entered into the eCRF and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Progenics or its representatives. This will be documented in a Clinical Study Agreement between Progenics, or designee and the investigator.

During the study, a monitor from Progenics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor, or designee.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor, or designee, and those SAEs that met criteria for reporting have been forwarded to the IRB.
- Confirm serious/unexpected/related SAE notification letter(s) from the Sponsor have been acknowledged and returned to the Sponsor.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact Progenics immediately if contacted by a regulatory agency about an inspection, and will provide Progenics with the results of any such audits and with copies of any regulatory documents related to such audits.

14. ETHICS

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirement(s). The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

14.1. Good Clinical Practice (GCP), Laws and Regulations

The investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

14.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit documented approval to the Sponsor before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor, or designee, will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

14.4. Subject Confidentiality

The Investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their date of birth and subject number on the case report forms or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

Written authorization is to be obtained from each subject prior to enrollment into the study in accordance with the applicable privacy requirements [e.g., the Health Insurance Portability and Accountability Act of 1996 Standards for Privacy of Individually Identifiable Health Information ("HIPAA") and any other state and country privacy requirements].

14.5. Financial Disclosure

All investigators must provide financial disclosure information in accordance with the US Code of Federal Regulations Title 21 CFR 54.2 through 54.6.

15. DATA HANDLING AND RECORDKEEPING

15.1. Case Report Forms and Study Records

Progenics or designee will provide an electronic case report form (eCRF) and eCRF Completion Guidelines for the entry of study data. eCRFs must be completed for each subject. All study data must be reported accurately on eCRFs from original source data. Source documents are original documents, data and records (e.g., hospital records, office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, magnetic media, diagnostic images, subject files). The investigator will make available the source documents for inspection. This information will be considered as confidential.

The use of eCRFs will encompass electronic data entry, query management and investigator approval. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines.

The Investigator or designee will review, sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the eCRF and will certify its content.

15.2. Inspection of Records

The Sponsor, or designee, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct. See Section 13.2.

15.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the

discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records. No study document should be destroyed without prior written agreement between Sponsor and the investigator.

16. PUBLICATION AND DISCLOSURE POLICY

All unpublished documentation [including the protocol, eCRF and Investigator Brochure (IB)] given to the investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of Progenics. The submission of these documents to the IRB is expressly permitted.

The investigator agrees that Progenics maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by Progenics in accordance with the guidelines set forth in the applicable publication or financial agreement.

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