CLINICAL STUDY PROTOCOL

Study Number:	PyL 3301
Study Title:	A Phase 3, Multi-**C**enter, **O**pen-Label Study to Assess the Diag**N**ostic Performance and Clinical Impact of ^{18}F-**D**CFPyL PET/CT Imaging Results in Men with Suspected Recurrence of Pr**O**state Cance**R** (**CONDOR**)
Product Name:	^{18}F-DCFPyL (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 31, 2018
	NCT03739684

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

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Protocol Version: Original: July 31, 2018

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]	[redacted]
Medical Monitor	[redacted]	[redacted]

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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
ADT	androgen deprivation therapy
AUA	American Urological Association
BCR	biochemical recurrence
BP	blood pressure
CFR	Code of Federal Regulations
CLR	Correct Localization Rate
CRF/eCRF	case report form/electronic case report form
CT	computed tomography
DMC	Data Monitoring Committee
FAS	Full Analysis Set
FDA	Food and Drug Administration
^{18}F	Fluorine-18
PyL	^{18}F-DCFPyL
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
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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
KeV	kiloelectron volt
kg	kilogram
mAbs	monoclonal antibodies
MBq	megaBequerel
mCi	milliCurie
MDP	methylene diphosphonate bone scan
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMQ	Medical Management Questionnaire
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
ng	nanogram
nM	nanomol
NPV	negative predictive value
PC	prostate cancer
PET	positron emission tomography
PI	Principal Investigator
PPV	positive predictive value
PSA	prostate specific antigen
PSADT	PSA doubling time
PSMA	prostate-specific membrane antigen
PT	preferred term
RP	radical prostatectomy
RT	Radiation Therapy
SAE	serious adverse event
SPECT	single photon emission computed tomography
SOC	Standard of Care
SUV	Standardized uptake value
US	United States/Ultrasound

1. BACKGROUND & RATIONALE

1.1. Background

Prostate cancer is the most common cancer among men in the United States (US) with an estimated annual incidence of 161,360 cases; 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 and/or recurrent disease.[2] Conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), [^{99m}Tc] methylene diphosphonate (MDP) bone scan, or ultrasound are not able to determine the location of recurrent and/or metastatic prostate cancer, particularly at low prostate specific antigen (PSA) levels.[3,4,5,6] Thus, imaging agents and modalities that will detect and localize the tumor, as well as small metastatic lesions, with high sensitivity and specificity are essential to more accurately diagnose and stage the disease, detect recurrence and metastases, and potentially monitor therapeutic response.

A number of new, targeted positron emission tomography (PET) tracers have been introduced for imaging prostate cancer.[7,8,9,10,11,12] A novel, high specific activity, highly selective, low-molecular weight prostate-specific membrane antigen (PSMA)-targeted PET radiotracer, ^{18}F-DCFPyL , has been investigated as an imaging agent for prostate cancer. Progenics has in-licensed^{18}F-DCFPyL (PyL) from Johns Hopkins University (JHU) in 2015; and Progenics plans to complete the clinical development program of PyL for the detection of recurrent and/or metastatic prostate cancer.

Refer to the Investigator's Brochure (IB) for detailed information on ^{18}F-DCFPyL Injection.

1.1.1. Pharmaceutical and Diagnostic Background

^{18}F-DCFPyL (PyL) is a small molecule radiolabeled with the positron-emitting radionuclide ^{18}F and binds to the extracellular domain of PSMA with high affinity. PSMA 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.[13,14] Since PSMA is expressed by virtually all prostate cancers, it is a very attractive target for developing agents for the diagnosis and staging of this disease.[15,16,17] In addition to high expression in malignant prostatic tissue and being directly related to tumor aggressiveness,[18] 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,[19,20] and in the neovasculature of nonprostatic solid carcinomas (e.g., renal cell, breast, colon, pancreas, melanoma, and lung carcinoma).[13,21]

Radiolabeled anti-PSMA monoclonal antibodies (mAbs) have been used to detect prostate cancer nodal metastasis and recurrence. Although the use of radiolabeled anti-PSMA mAbs have been met with logistical and clinical limitations as an imaging agent, phase 1 and 2 therapeutic trials utilizing PSMA as a therapeutic target have shown early promising results.[22,23] Nonetheless, 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 ratio and thereby making lesion detection more conspicuous. In the past several 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, ^{99m}Tc-MIP-1404,[24, 25, 26] has just completed its phase 3 study enrollment for the detection of clinically significant prostate cancer in patients with low grade disease. PET imaging agents, such as ^{124}I-MIP-1095, ^{18}F-DCFCBC, ^{18}F-DCFPyL, ^{18}F-FACBC and ^{68}Ga-HBED-CC, have also generated much interest for their potential use in detecting metastatic prostate cancer. Of these, ^{68}Ga-HBED-CC (^{68}Ga-PSMA) has been more broadly studied at academic centers and mostly under retrospective protocols.

^{18}F-DCFPyL ("PyL") has been the subject of extensive investigation since its synthesis and characterization by investigators at JHU in 2011.[27,28] Over the past few years, various versions of PyL have been synthesized and used in academic investigator-sponsored studies and on a compassionate use basis in the US, Canada, and Europe. Collectively, published study results suggest that ^{18}F-DCFPyL PET/CT provide high image quality and visualize small prostate lesions with excellent sensitivity.[29,30,31,32,33] Furthermore, F-18 tracers offer important practical advantages, including higher production capacity than PET radiopharmaceuticals labeled with other radionuclides, such as Ga-68, which would facilitate rapid patient access. The detection rate of ^{18}F-DCFPyL PET/CT compares favorably with that of ^{68}Ga-PSMA PET/CT in patients with biochemical recurrence (BCR).[34] The results of the Dietlein *et al* study also showed that ^{18}F-DCFPyL PET/CT provided high image quality and visualized small prostate lesions with excellent sensitivity. Thus, ^{18}F-DCFPyL PET/CT promises to be a useful diagnostic to localize prostate cancer, including in patients with suspected recurrence of prostate cancer where there is a high unmet medical need.

1.1.2. Nonclinical Studies

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. Data from an 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.

1.1.3. Previous Human Experience

Several investigator-initiated clinical studies with ^{18}F-DCFPyL Injection have been completed at JHU under IND 121,064. Data from two completed clinical studies show that PET imaging with ^{18}F-DCFPyL Injection is feasible and safe. Study J1418 was 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 was 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 (SOC) therapy.

Biodistribution following administration of ^{18}F-DCFPyL Injection and an optimal imaging time point were determined, and the radiation dose used was within limits for diagnostic radiotracers for PET.[28,31] 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.[32,33] Sensitivity and specificity with ^{18}F-DCFPyL PET/CT in patients with at least localized intermediate risk prostate cancer who have undergone radical prostatectomy (RP) with lymphadenectomy was comparable to published ^{68}Ga-PSMA imaging data.[30,35]

1.1.4. Ongoing Progenics-Sponsored Clinical Trial(s)

An open-label, non-randomized, phase 2/3, multi-center study (PyL 2301) is being conducted in the US and Canada to evaluate the safety and diagnostic performance of ^{18}F-DCFPyL PET/CT imaging in patients with at least high-risk localized or metastatic prostate cancer. The study is entitled, 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; NCT02981368). Eligible subjects with at least high-risk prostate cancer defined by NCCN v.3.2016 who are planned for radical prostatectomy with pelvic lymph node dissection (cohort A), and subjects with radiologic evidence of local recurrence or new or progressive metastatic disease (cohort B) are enrolled and administered 9 mCi (333 MBq) ^{18}F-DCFPyL Injection followed by PET/CT imaging within 1-2 hours post-dosing. Diagnostic performance characteristics of ^{18}F-DCFPyL PET/CT imaging will be evaluated using histopathology as the truth standard. Overall, ^{18}F-DCFPyL imaging agent has been well-tolerated.

For study details and current safety findings please refer to the IB for ^{18}F-DCFPyL Injection.

1.2. Rationale for the Study

One of the most challenging aspects of the clinical management of prostate cancer is the development of disease recurrence after prostatectomy, radiotherapy, or other local treatment modalities.[36, 37, 38] Disease recurrence (rising PSA) after initial definitive therapy, defined as a confirmed PSA value of $\geq$ 0.2 ng/mL after prostatectomy or $\geq$ 2 ng/mL above nadir after

radiation therapy, is known as biochemical recurrence (BCR) of prostate cancer.[39 40] BCR after initial therapy may develop in 20-30% of patients.[36,37] Although PSA is the primary biomarker for recurrence, its values cannot determine the location or the extent of disease burden of recurrent and/or metastatic disease. PSA kinetics, such as PSA velocity as measured by PSA doubling time (PSADT), are helpful in early detection of occult disease, however they still cannot differentiate between local, regional, or systemic disease to guide further disease management.

The transition to a state of evident metastatic disease (M1) on imaging represents a significant clinical event for both the patients and their treating physicians. Conventional imaging modalities all have low sensitivity and are not able to determine the location of recurrent or metastatic prostate cancer, particularly at low PSA levels.[4,5,6,7] Thus, imaging agents and modalities that will detect and localize small metastatic lesions, with high sensitivity and specificity, are essential to more accurately diagnose and stage the disease, inform the best treatment strategy and potentially monitor therapeutic response. Early diagnosis of disease recurrence is essential as exemplified by analyses of outcomes post salvage radiotherapy, which is most effective when initiated at PSA levels < 0.5 ng/ml.[41, 42, 43]

A number of radiopharmaceutical PET imaging agents have been explored for the detection of prostate cancer, and studied particularly in BCR patients, including 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), ^{11}C-Choline, ^{18}F-FACBC (^{18}F-fluciclovine; Axumin), ^{68}Ga-HBED-CC (^{68}Ga-PSMA-11), and ^{18}F-DCFPyL.[7,11,44 ,45, 46, 47, 48, 49] FDG PET, the clinical standard for a number of cancers, has demonstrated mixed results in imaging prostate cancer.[7,10] Other tumor metabolism-based approaches are the use of radiolabeled choline to take advantage of the increased expression of choline kinase (ChKα) in tumor cells, or increased uptake of amino acids such as methionine or leucine.[8,9] Although ^{11}C choline was approved by FDA in the BCR setting in 2012, its sensitivity appears limited for extraprostatic lesions and has low detection rates for PSA < 1 ng/mL.[50,51,52,53] ^{18}F-fluciclovine (synthetic L-leucine analog trans-1-amino-3-^{18}F-fluoro-cyclobutane carboxylic acid) PET/CT imaging has been studied in recurrent prostate cancer as well as suspected recurrent prostate cancer;[46 47 5455] it was approved by the FDA in 2016 in patients with rising PSA after initial definitive therapy.[56] However, the detection rate of ^{18}F-fluciclovine seems to be affected by PSA levels, with higher chance of false positive scans in patients with PSA < 1.8 ng/mL.[54 56]

The recognition of PSMA as a relatively specific biomarker for prostate cancer has resulted in the development of several diagnostic compounds currently under clinical investigation, with the promise of better sensitivity to detect early, more likely curable stages of metastatic or recurrent prostate cancer. PSMA is highly expressed in castration-resistant, metastatic prostate cancer.[21] A retrospective evaluation of data from ^{68}Ga-PSMA PET/CT imaging in the BCR setting showed 58% detection rate, even in patients with low PSA (0.2 to <0.5 ng/ml).[48] Studies have also compared ^{68}Ga-PSMA PET and ^{18}F-choline PET imaging, and ^{68}Ga-PSMA PET versus ^{18}F-fluciclovine PET in prostate cancer.[57 58,59] Comparison of ^{68}Ga-PSMA PET to both PET-imaging agents showed significantly higher detection rate and diagnostic accuracy with ^{68}Ga-PSMA PET in prostate cancer, including patients with recurrent prostate cancer as well as those with suspected recurrence (BCR).[49,58]

Nevertheless, fluorine-18 (F-18) PET tracers offer important advantages over PET tracers labeled with other radionuclides, including Ga-68, such as higher production capacity, longer half-life, and improved image resolution. Thus, ^{18}F-DCFPyL, a PSMA PET-imaging agent, promises to be a useful diagnostic candidate for the detection of metastatic or recurrent prostate cancer, including in the BCR setting where there remains a high unmet medical need.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. Primary Objective

To determine the Correct Localization Rate (CLR) of ^{18}F-DCFPyL PET/CT imaging in the detection of recurrent prostate cancer at the subject level

2.2. Secondary Objectives

1. To assess the impact of ^{18}F-DCFPyL PET/CT disease detection on patient's clinical management plans
2. To evaluate the safety and tolerability of ^{18}F-DCFPyL

2.3. Exploratory Objectives

1. To determine detection rates of disease sites with ^{18}F-DCFPyL PET/CT by region (prostatic, pelvic, extra-pelvic) and baseline PSA
2. To determine the Positive Predictive Value (PPV) of ^{18}F-DCFPyL PET/CT imaging in the detection of recurrent disease in the prostatic, pelvic, and extra-pelvic regions

3. TRIAL ENDPOINTS

3.1. Primary Endpoint

The CLR at the subject level, defined as the percentage of subjects for whom there is a one-to-one correspondence between localization of at least one lesion identified on ^{18}F-DCFPyL PET/CT imaging and the composite truth standard (See Section 8.1)

3.2. Secondary Endpoints

3.2.1. Secondary Efficacy Endpoints

- The percentage of subjects with a change in intended prostate cancer treatment plans due to ^{18}F-DCFPyL PET/CT as measured by comparison of intended management questionnaires completed Pre- and Post- ^{18}F-DCFPyL PET/CT imaging results

3.2.2. Safety Endpoints

- Incidence of treatment-emergent adverse events from time of ^{18}F-DCFPyL dosing up to 7 (±3) days following ^{18}F-DCFPyL dosing
- Change from Baseline to post ^{18}F-DCFPyL injection vital signs

- Concomitant medications and medical procedures

3.3. Exploratory Endpoints

- The detection rates of ^{18}F-DCFPyL PET/CT among lesion locations i.e., prostatic, pelvic, extra-pelvic
- The PPV of ^{18}F-DCFPyL PET/CT for prostatic, pelvic, extra-pelvic regions from the composite truth standard in subjects with positive lesion(s) on ^{18}F-DCFPyL PET/CT imaging
- The percentage of subjects with positive ^{18}F-DCFPyL PET/CT scans who have negative findings for prostate cancer based on the composite truth standard
- The detection rates of ^{18}F-DCFPyL PET/CT imaging as a function of baseline PSA groups

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a phase 3, multi-center, open-label, single-arm, non-randomized study to evaluate the diagnostic performance and safety of ^{18}F-DCFPyL (PyL) PET/CT in subjects with suspected recurrence of prostate cancer and negative or equivocal findings per institutional standard of care conventional imaging. This study is planned to be conducted in approximately 15 sites in the United States and Canada, and to be conducted in conformance with Good Clinical Practices (GCP).

Eligible subjects (see Section 5 for Eligibility Criteria) will be enrolled in a non-randomized, sequential manner, with competitive enrollment between study sites. Enrolled subjects will receive a single dose of 9 mCi (333 MBq) ^{18}F-DCFPyL Injection followed by a single PET/CT scan acquired at 1-2 hours post-dosing.

Only subjects with positive PyL PET/CT scans (detection of disease at any site) will be followed at the Efficacy visit(s) (See Table 3 Schedule of Assessments). Subjects will undergo Efficacy follow-up based on their PyL PET/CT finding(s) per local interpretation and clinical presentation for evaluation of the composite truth standard as defined in Section 8.1.

If biopsy or surgery of a lesion identified on PyL PET/CT is feasible, attempts will be made to obtain tissue corresponding to the PyL-suspected lesion(s) within 60 days following PyL PET/CT imaging. If local histopathology results are obtained, they will be recorded in the eCRF and if the results are evaluable for prostate cancer, the subject will complete the study.

If histopathology (from biopsy or surgery) is not evaluable, or biopsy or surgery of the PyL-suspected lesion was not performed, an attempt will be made to anatomically correlate the PyL-suspected lesion(s) with conventional imaging modality per the Investigator's discretion within 60 days following PyL PET/CT imaging. The conventional imaging scan will be sent to the central imaging core lab for review. If the scan is deemed evaluable by the central imaging core lab, the subject will complete the study.

If evaluable histopathology is not available and conventional imaging of the PyL-suspected lesion(s) is not informative, those subjects who are planned to receive locoregional RT without concomitant androgen deprivation therapy (ADT) within 60 days following PyL PET/CT imaging will continue on-study and be followed for PSA changes following RT alone. PSA (total) will be collected every 3 months post-RT alone (until Response is achieved as defined in Section 8.1, for a maximum of up to 9 months total duration) and sent to the central lab for analysis. All other subjects not initiated on locoregional RT alone within 60 days post PyL PET/CT imaging will be discontinued from the study.

Subjects who are initiated on any systemic therapy for prostate cancer (PC) will be discontinued from the study.

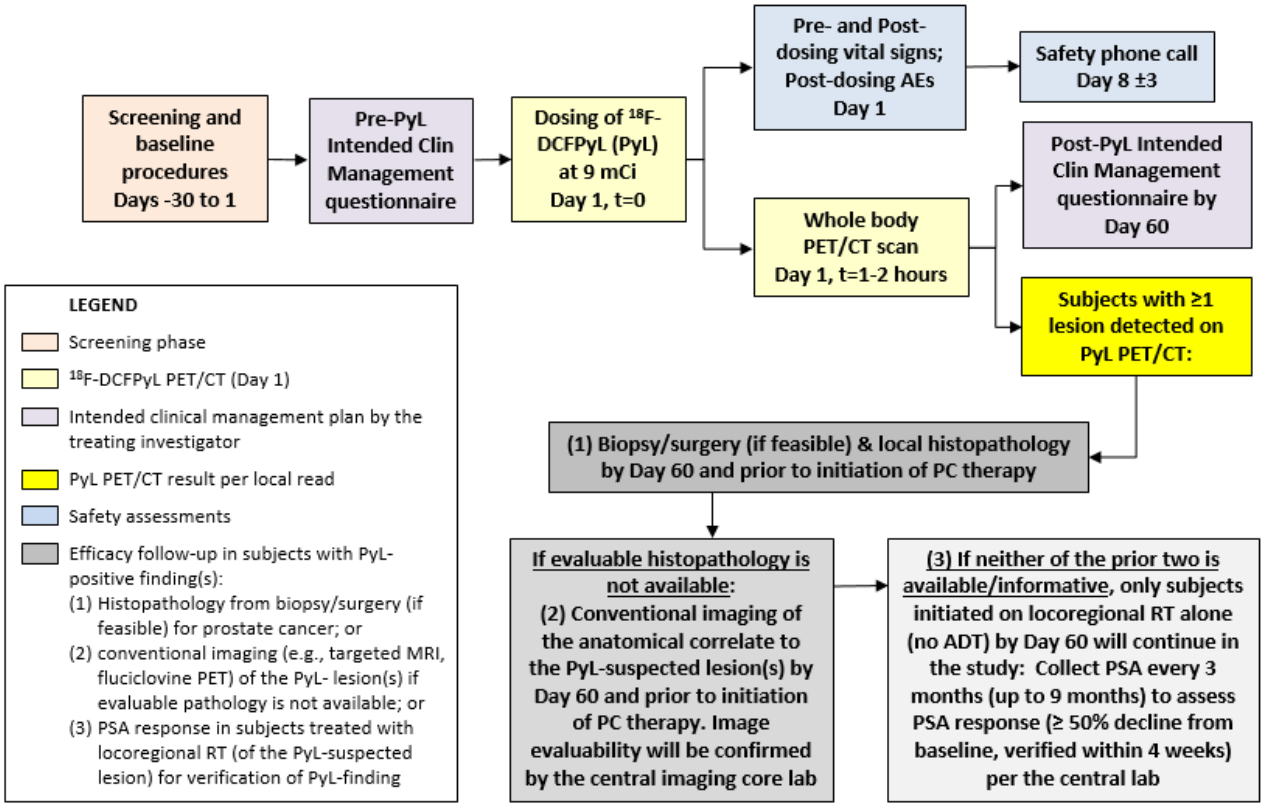
Once the study reaches the required number of subjects evaluable for calculation of the primary endpoint as described in Section 10.4.2 , subject enrollment and follow-up assessments will conclude, and the study database will be locked for analysis. Adverse events (AEs) will be assessed following ^{18}F-DCFPyL dosing (Day 1), and again via a safety phone call 7 (±3) days post-^{18}F-DCFPyL dosing to capture any late-occurring AEs.

Medical Management Questionnaires (MMQs) will be completed by the treating investigator at two time-points during the study to capture intended changes in the clinical management for all subjects who underwent ^{18}F-DCFPyL PET/CT imaging:

- **Prior to ^{18}F-DCFPyL dosing,** the treating investigator will complete the Pre-PyL MMQ based on baseline clinical information and results from conventional imaging.
- **Post-^{18}F-DCFPyL imaging**, the treating investigator will complete the Post-PyL MMQ based on the additional result from local interpretation of the ^{18}F-DCFPyL PET/CT scan, to assess whether an intended change to the initial medical management plan is warranted due to the PyL finding.

See Figure 1 and Table 3 for the study schema and schedule of study assessments. Details on study procedures for each visit are described in Section 4.3.

Figure 1: Study Schema



4.2. Number of Subjects

Approximately 200 subjects are planned to be enrolled in this study to meet the number of subjects required for assessment of the primary endpoint. The Sponsor will periodically monitor the rate of positive ^{18}F-DCFPyL PET/CT scans and the number of evaluable subjects that contribute to the efficacy assessment. If the observed rate of positive ^{18}F-DCFPyL PET/CT scans is lower than expected, the sample size may need to be increased. When the required number of subjects are evaluable for calculation of the primary endpoint, subject enrollment and follow-up assessments will conclude.

See Section 5 for eligibility criteria and Section 10.1 for complete sample size assumptions.

4.3. Study Procedures

See Figure 1 for the study schema and Table 3 Schedule of Assessments for a comprehensive summary.

4.3.1. Screening (Day -30 to 1)

The following screening procedures and assessments must be completed prior to ^{18}F-DCFPyL dosing and PET/CT imaging (Day 1):

- Obtain informed consent

- Demographic information, including date of birth, race, ethnicity, height and weight
- Clinically relevant medical history
- Prostate cancer history, including disease history, staging, and treatment(s)
- Conventional imaging findings per institutional standard of care (SOC) scan(s) (e.g., pelvic CT/MRI, whole-body bone scan, NaF, fluciclovine or choline PET) completed within 60 days prior to Day 1. SOC scan(s) performed more than 60 days prior to Day 1 may be repeated as a study Screening procedure and reviewed by the investigator prior to Day 1.

Subjects who provide signed informed consent and meet all eligibility criteria during Screening must also complete the following additional procedures prior to ^{18}F-DCFPyL dosing PET/CT imaging (Day 1):

- Obtain a blood draw for PSA (total) and send to the central lab. If done on Day 1, the blood draw should be collected prior to ^{18}F-DCFPyL dosing.
- The treating investigator completes the Pre-PyL Medical Management Questionnaire (MMQ) to document the initial intended management plan for the subject based on available clinical information and local conventional imaging results.

4.3.2. ^{18}F-DCFPyL – Dosing and PET/CT Imaging (Day 1)

Subjects will visit the clinic for ^{18}F-DCFPyL dosing and whole-body PET/CT imaging on Day 1.

Prior to receiving ^{18}F-DCFPyL Injection, perform the following:

- Measure vital signs (blood pressure and heart rate);
- Record current medications and procedures and note changes from Screening.

All subjects are to receive a prescribed dose of 9 mCi (333 MBq) ^{18}F-DCFPyL Injection. Dosing adjustments of ^{18}F-DCFPyL are not permitted. See Section 7.6 Study Drug Administration for details.

After dosing of ^{18}F-DCFPyL Injection and within approximately 60-120 minutes post-^{18}F-DCFPyL dosing, perform the following:

- Measure vital signs (blood pressure and heart rate);
- Acquire a single PET/CT scan from mid-thigh to skull (See Imaging Manual for guidelines);
- Record treatment-emergent adverse events (AEs) and any new medications and/or procedures since prior to ^{18}F-DCFPyL dosing.

The site's local interpretation of ^{18}F-DCFPyL PET/CT results will be recorded in the eCRF. See the Imaging Manual for ^{18}F-DCFPyL PET/CT interpretation guidelines.

4.3.3. Safety Follow-up (phone call; Day 8 [±3])

A safety phone call at 7 (±3) days post-^{18}F-DCFPyL dosing is required for all subjects who received any dose of ^{18}F-DCFPyL to capture any late-occurring AEs and concomitant

medications and procedures. If Efficacy follow-up occurs within 7 (±3) days post-^{18}F-DCFPyL dosing, the Safety phone call will not be completed, and the late-occurring AEs and concomitant medications and procedures will instead be collected at the time of the Efficacy follow-up.

See Section 9 Assessment of Safety for complete details.

4.3.4. Post-PyL Intended Management Plan (Day 2-60)

For all subjects who complete the PyL PET/CT scan, the Post-PyL MMQ will be completed by the treating investigator based on the additional result from the local PyL PET/CT scan to document whether a change to the initial intended management plan may be warranted due to the PyL finding. The Post-PyL MMQ should be completed within 60 days following ^{18}F-DCFPyL PET/CT imaging.

4.3.5. Efficacy Follow-up (Performed or Initiated by Day 2-60)

Only subjects with positive PyL PET/CT scans (detection of disease at any site) per local interpretation will continue to be followed for verification of PyL-suspected lesion. Subjects who do not have a positive PyL PET/CT result will have completed the study after completing the Safety follow-up.

4.3.5.1. Verification of PyL-suspected lesion (per local PyL PET/CT finding)

Subjects with at least one positive lesion identified per local PyL PET/CT imaging will undergo Efficacy follow-up for the composite truth standard as defined in Section 8.1. Concomitant medications and procedures will be collected at the time of the Efficacy follow-up visit(s). See Table 3 Schedule of Assessments.

Biopsy or Surgery within 60 days following ^{18}F-DCFPyL PET/CT

At least 12 hours from time of ^{18}F-DCFPyL dosing and no more than 60 days following PyL PET/CT imaging (Day 1) and prior to initiation of any radiation or systemic therapies for prostate cancer, an image-guided biopsy or surgery (e.g. salvage pelvic lymph node dissection) of a lesion identified by PyL PET/CT scan is encouraged if clinically feasible.

For subjects undergoing image-guided needle biopsy, the needle biopsy images (e.g., CT, TRUS-MRI, US) of the procedure will be sent to the central imaging core lab.

Local histopathology results of tissue(s) obtained will be recorded in the eCRF. Subjects with an evaluable histopathology result for prostate cancer will have completed the study. If evaluable histopathology result is not available, then subjects will undergo conventional imaging follow-up within 60 days following ^{18}F-DCFPyL PET/CT imaging. See Section 8 Assessment of Efficacy.

Conventional imaging within 60 days following ^{18}F-DCFPyL PET/CT

If biopsy or surgery is not clinically feasible on a lesion identified by PyL PET/CT scan, conventional imaging based on the Investigator's discretion (e.g., targeted MRI or CT; fluciclovine or choline PET) on the PyL-suspected lesion will be performed and sent to the central imaging core lab. The choice of the most appropriate conventional imaging modality will be at the discretion of the investigator; use of the most sensitive imaging method is encouraged, such as targeted MRI for verification of the PyL-suspected bone lesion(s).

Subjects with informative conventional imaging of the anatomical correlate to the PyL-suspected lesion(s) based on central imaging core lab review will have completed the study.

See Section 8 Assessment of Efficacy.

Initiation of locoregional radiation therapy (RT) in subjects without evaluable histopathology result or informative conventional imaging of the PyL-suspected lesion(s) within 60 days following ^{18}F-DCFPyL PET/CT

If an evaluable histopathology result for prostate cancer is not available and follow-up conventional imaging of the PyL-suspected lesion is not informative, subjects initiated on locoregional RT alone (no concomitant ADT) within 60 days following PyL PET/CT imaging will be followed every 3 months (± 7 days) for up to an additional 9 months to assess PSA response to RT alone (without concomitant ADT administered during this time). To be evaluable for PSA response, applicable subjects should undergo RT with fields and target volumes adjusted based on presence of PyL-positive prostate bed, pelvic nodal, visceral or limited osseous metastases.

A blood draw for PSA (total) will be obtained and sent to the central lab at each follow-up assessment. PSA response is defined by decline of ≥ 50% from baseline PSA and must be confirmed within 4 weeks. Subjects will complete follow-up within the 9-month duration once PSA response is confirmed per the central lab.

Concomitant medications and procedures will be collected. See Section 8 Assessment of Efficacy.

4.4. Study Duration

Subjects will be deemed enrolled once they sign informed consent and meet all inclusion and no exclusion criteria and complete all screening assessments. The study duration of subject participation from Screening through ^{18}F-DCFPyL PET/CT imaging and Efficacy visit(s), if applicable, will be a maximum duration of approximately 12 months. At a minimum, all subjects who receive a dose of ^{18}F-DCFPyL will be followed from time of informed consent until the safety phone call on Day 8 (± 3).

Only subjects with positive PyL PET/CT scans (detection of disease at any site) will be followed at the Efficacy visit(s). Subjects will undergo Efficacy assessments based on the site's local PyL PET/CT interpretation and clinical presentation.

- Subjects with any positive PyL PET/CT finding(s) per local interpretation will be evaluated as described in Section 4.3.5.
- Subjects without any positive PyL PET/CT finding per local interpretation will complete the study through the safety phone call; no further visits will be required.

The Sponsor may conclude the study before subjects complete their efficacy follow-up assessments (see Section 10.4.2)

4.5. 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 9. A safety review committee, consisting of Sponsor representatives (e.g., Medical Monitor, Clinical, Drug Safety) will also review data on an ongoing basis to assess subject safety and eligibility through listings, tables and subject profiles.

4.6. 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 Independent Ethics Committee (IEC) may terminate an investigational site for the following (but not limited to) reasons:

- If any significant 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 significant 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	^{18}F-DCFPyL Dosing & Imaging		Safety Phone call[3]	Efficacy follow-up[4]	
Day	**-30 to 1**	**1**	**1 (60-120 min post-dosing)**	**8 (±3)**	**2 to 60**	**Every 3 months following initiation of locoregional RT, up to 9 months[7]**
Informed Consent & Eligibility	X					
Demographics	X					
Medical History	X					
Prior Medications and Prior Cancer Treatments	X					
Vital Signs (blood pressure, heart rate)		X (pre-dosing)	X			
PSA (Total)	X[1]					X[1,7]
Conventional imaging	X[2]				X[6]	
^{18}F-DCFPyL Administration		X				
Whole body PyL PET/CT			X			
Surgery or image-guided biopsy & histopathology					X[5]	
Locoregional radiation therapy per investigator discretion					X[7]	
Treatment-emergent Adverse Events		X		X		
Concomitant Medications and Procedures		X		X	X	X
Medical Management Questionnaire	X[8]				X[9]	

1. Total PSA will be collected and sent to central lab for analysis. If done on Day 1 of Screening, the blood draw should be collected prior to ^{18}F-DCFPyL dosing.
2. Applicable conventional imaging performed as part of standard of care workup within 60 days prior to Day 1.
3. A safety phone call will occur 7 (±3) days post-^{18}F-DCFPyL dosing if Efficacy follow-up has not yet occurred.
4. Efficacy follow-up visit(s) are only applicable for subjects with positive ^{18}F-DCFPyL PET/CT finding(s) per local interpretation
5. Surgery or biopsy to occur at least 12 hours from time of ^{18}F-DCFPyL dosing but not more than 60 days following ^{18}F-DCFPyL PET/CT imaging. Imaging used to guide biopsy (e.g., CT, MRI-TRUS, US) will be submitted to the central core imaging lab.
6. Follow-up conventional imaging (e.g., targeted MRI/CT, fluciclovine or choline PET) per Investigator's discretion of the anatomical correlate to the lesion(s) identified on 18F-DCFPyL PET/CT is required in subjects whom evaluable histopathology for prostate cancer is not available. The image(s) will be submitted to the central core imaging lab for review and determination of evaluability.
7. If evaluable histopathology result for prostate cancer is not available and follow-up conventional imaging of the PyL-suspected lesion is not informative, subjects initiated on locoregional radiation therapy (RT) alone within 60 days following PyL PET/CT (with no concomitant ADT administered during this time) will be followed every 3 months (± 7 days), up to 9 months post-initiation of RT. PSA response (decline of ≥50% from baseline PSA) must be confirmed (two consecutive levels within 4 weeks) per central lab evaluation.
8. Pre-PyL Medical Management Questionnaire (MMQ) will be completed by the treating investigator for all subjects enrolled (who signed informed consent and met all eligibility criteria) in the study prior to Day 1.
9. Post-PyL MMQ will be completed by the treating investigator for all subjects who completed ^{18}F-DCFPyL PET/CT imaging.

5. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

5.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Male ≥ 18 years of age
2. Histopathologically confirmed prostate adenocarcinoma per original diagnosis, with subsequent definitive therapy
3. Suspected recurrence of prostate cancer based on rising PSA after definitive therapy on the basis of:
    a. Post-radical prostatectomy (RP): Detectable or rising PSA that is ≥ 0.2 ng/mL with a confirmatory PSA ≥ 0.2 ng/mL (American Urological Association [AUA] recommendation)[39]; or
    b. Post-radiation therapy (RT), cryotherapy, or brachytherapy: Increase in PSA level that is elevated by ≥ 2 ng/mL above the nadir (American Society for Therapeutic Radiology and Oncology [ASTRO]-Phoenix consensus definition)[40]
4. Negative or equivocal findings for prostate cancer on conventional imaging performed as part of standard of care workup within 60 days prior to Day 1
5. Life expectancy ≥6 months as determined by the investigator
6. Able and willing to provide informed consent and comply with protocol requirements

5.2. Subject Exclusion Criteria

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

1. Subjects administered any high energy (>300 KeV) gamma-emitting radioisotope within five (5) physical half-lives prior to Day 1
2. Ongoing treatment with any systemic therapy (e.g., androgen deprivation therapy [ADT], antiandrogen, GnRH, LHRH agonist or antagonist) for prostate cancer
3. Treatment with ADT in the past 3 months of Day 1
4. Receipt of investigational therapy for prostate cancer within 60 days of Day 1
5. Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise the safety or compliance of the subject to produce reliable data or completing the study

5.3. Subject Withdrawal Criteria

A subject may withdraw from the study at any time for any reason without prejudice to his 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
- 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 from the study, all efforts will be made to complete the required study procedures as thoroughly as possible prior to withdrawal.

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.

6. TREATMENT OF SUBJECTS

6.1. Description of Study Drug

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

Table 4: Investigational Product

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

6.2. Concomitant Medications and Procedures

All concomitant medications and medical procedures will be recorded in the eCRF from post-^{18}F-DCFPyL dosing (Day 1) and at all subsequent study visits as shown in Table 3 Schedule of Assessments.

Any new or changed medications, including prostate cancer therapy, from time of ^{18}F-DCFPyL injection to each study visit must be recorded in the eCRF. Subjects who receive concomitant systemic or investigational therapy for prostate cancer anytime during participation in the study will be discontinued from the study.

6.3. Treatment Compliance

All ^{18}F-DCFPyL injections 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.

6.4. Randomization and Blinding

This is an open-label, non-randomized study.

Independent readers from a central imaging core lab will be given access to ^{18}F-DCFPyL PET/CT, biopsy-guided imaging (if performed), and follow-up conventional imaging (if performed). The central readers will be blinded to all other clinical information and histopathology results (if available).

Institutional staff may review all local images in conjunction with available clinical information to permit clinical management planning for the subject. The informed consent form (ICF) must include language of potential changes to the medical management plan for the subject.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

Please reference Section 6.1 for a description of the study drug.

7.2. Restrictions

7.2.1. Food and Fluid Intake

There are no dietary or food restrictions for this trial.

Fasting is not required prior to ^{18}F-DCFPyL (PyL) dosing and PET/CT imaging. Increased fluid intake should occur before and after image acquisition to maintain proper hydration throughout the study period, decrease radiation exposure to the urinary bladder and improve image quality. Additionally, subjects should be encouraged to void as frequent as possible. At a minimum void post study drug injection, immediately before imaging, and after imaging.

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

7.2.2. Radioactivity

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

7.3. Study Drug Packaging and Labeling

The final drug product (^{18}F-DCFPyL) is a clear, particulate-free injectable solution at a strength of 1-90 mCi/mL (37-3330 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 shield unit-dose system and delivered to the clinical site.

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. "New Drug—Limited by Federal Law to Investigational Use" will be included on the prescription label of the lead shield unit-dose system for each unit-dose syringe.

7.4. Study Drug Storage

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

7.5. Study Drug Preparation

The final drug product is supplied to each institution on the day of administration in a unit-dose syringe (contained in the lead shield unit-dose system) with no additional preparation required. Institutional policies and procedures 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. Record the exact times of dose calibration and time of injection. The decay-corrected administered dose will be calculated in the electronic database management system when the dose measurements and times are entered in the eCRF. Please see the Imaging Manual for complete details including pre and post-injection measurement of the ^{18}F-DCFPyL Injection dose syringe

7.6. Study Drug Administration

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

- Place an IV catheter in an antecubital vein or an equivalent venous access.
- Ensure patency of the line with a saline flush.
- Inject a bolus of the prescribed dose of ^{18}F-DCFPyL (9 mCi or 333 MBq) of into the IV line or equivalent venous access by slow push from the appropriately shielded syringe according to normal local practices.
- 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:

- Try to aspirate as much extravasated drug as possible through the still-intact catheter. Any of the dose remaining should be measured and recorded to permit correction of the administered dose for radioactive decay.
- Imaging should proceed unless contraindicated for safety reasons.
- Notify the interpreting physician of the extravasation (location and estimated amount).
- Examine the skin area for local toxicity before discharge; instruct subject to contact site immediately if local symptoms at injection site do not improve or worsen.
- Note the extravasation as an Adverse Event in the eCRF.

7.7. 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 subject, 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 drug is 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 representative(s) and when appropriate, reconciliation will be performed.

7.8. 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 drug on the Drug Accountability record.

8. ASSESSMENT OF EFFICACY

8.1. Composite Truth Standard

Subjects will undergo Efficacy assessments based on their local PyL PET/CT finding(s) and clinical presentation for evaluation of the composite truth standard, defined either as:

1) evaluable local histopathology result for prostate cancer from surgery or biopsy performed within 60 days following PyL PET/CT, or
2) if evaluable histopathology is not available, informative conventional imaging (e.g., targeted MRI or CT; fluciclovine or choline PET) finding(s) of the anatomical correlate to the PyL-suspected lesion(s) within 60 days following PyL PET/CT, before locoregional or systemic treatment in started, or
3) if neither of the above is available or informative, confirmed PSA response (PSA decline by ≥50% from baseline, confirmed within 4 weeks per central lab evaluation) post-RT (no concomitant ADT) that was initiated within 60 days following PyL PET/CT. PSA will be collected every 3 months, up to 9 months until PSA response (if achieved) is confirmed.

8.2. Image Acquisition

Central imaging core lab readers will independently assess all PyL PET/CT images as well as any subsequent conventional images performed following PyL PET/CT.

8.2.1. Follow-up conventional imaging to verify PyL-suspected lesion(s) within 60 days following ^{18}F-DCFPyL PET/CT

Within 60 days following ^{18}F-DCFPyL PET/CT imaging, if a positive lesion(s) is identified on ^{18}F-DCFPyL PET/CT and tissue acquisition of the PyL-suspected lesion is not feasible, then conventional imaging (e.g., targeted MRI or CT, fluciclovine or choline PET) will be performed in an attempt to anatomically correlate the PyL-suspected lesion(s). All follow-up imaging will be sent to the central imaging core lab. The choice of the most appropriate conventional imaging modality will be at the discretion of the investigator; use of the most sensitive imaging method is encouraged, such as targeted MRI for verification of the PyL-suspected bone lesion(s).

If tissue acquisition (by surgery or biopsy) of the PyL-suspected lesion is feasible, then see Section 8.4 Histopathology.

8.2.2. ^{18}F-DCFPyL PET/CT Imaging

Prior to enrollment, all PET/CT scanners to be used in this study must be qualified in accordance with the procedures outlined in the Imaging Manual.

^{18}F-DCFPyL PET/CT imaging will be performed using local PET/CT scanners with low dose CT for attenuation correction and anatomic localization as described in the Imaging Manual. Subjects will be asked to void prior to imaging. After voiding, a whole-body CT and PET scan will be acquired starting from the mid-thigh through the skull. Whole body PET/CT scans must be obtained within 60-120 minutes following the ^{18}F-DCFPyL dosing.

All ^{18}F-DCFPyL PET emission data should be acquired and reconstructed in accordance with the Imaging Manual.

8.2.3. Imaging at Biopsy (if biopsy is performed)

If a ^{18}F-DCFPyL (PyL) PET-positive lesion is feasible for biopsy, then an image-guided biopsy should be performed on the amenable lesion. The imaging modality (e.g., CT, MRI-TRUS, US) used to guide biopsy will be collected in the eCRF. The image obtained at biopsy will be submitted for central review to confirm the anatomical location of interest correlates with the lesion identified on the PyL PET/CT.

The instruction for capturing biopsy images and directions for submitting the images to the central imaging core lab is found in the Imaging Manual.

8.3. Image Interpretation by Central Imaging Core Lab

The central imaging core lab will receive and evaluate all conventional images and PyL PET/CT scans, as applicable. Imaging data will be anonymized at the site upon image submission to the central lab and prepared for reading. PET data will be interpreted by three different independent readers in a random order at separate reading sessions. Cross sectional CT imaging from the PET/CT scans will be available for anatomic correlation. Central imaging core lab readers will be blinded to all clinical data, including PSA and histopathology (if available).

The processes for image acquisition, transmittal and interpretation are detailed in the Imaging Manual and Imaging Review Charter documents.

8.4. Histopathology from Biopsy or Surgery (if performed) of PyL-positive lesion(s) within 60 days following ^{18}F-DCFPyL PET/CT

Within 60 days following PyL PET/CT imaging and prior to initiation of any new systemic or radiation PC therapy, if a PyL-positive lesion is identified per the site's image interpretation, tissue acquisition via surgery or image-guided biopsy should be performed if clinically feasible.

Immediately following biopsy or surgery, the specimens will be sent for local histopathological processing and analysis at the site in accordance with the study Pathology Manual. Procedures and results will be recorded in the eCRF. See Section 8.4 for histopathology processing and analysis at the site. If the subject's histopathology result is evaluable for prostate cancer, then no further visits are required for the subject. If histopathology is not evaluable, then see Section 8.2.1 for required conventional imaging follow-up.

8.4.1. Image-Guided Biopsy (if feasible) of PyL-positive lesion

Image-guided (e.g., CT, MRI-TRUS, US) needle biopsy of a PyL-positive lesion is highly encouraged if clinically feasible. If tissue acquisition of a PyL-positive lesion is not feasible, see Section 8.2.1 for required conventional imaging follow-up.

See Section 8.2.3 for instructions on image at biopsy and Section 8.3 for submitting the images to the central imaging core lab.

8.5. PSA (total) Response

If evaluable histopathology result for prostate cancer is not available and follow-up conventional imaging of the PyL-suspected lesion is not informative, subjects initiated on locoregional RT

alone (no concomitant ADT within 60 days following PyL PET/CT imaging) will be followed every 3 months for up to an additional 9 months post initiation of RT to assess PSA response to RT alone (without concomitant ADT administered during this time). A blood draw for PSA (total) will be obtained and sent to the central lab at each follow-up assessment. PSA response is defined by decline of ≥ 50% from baseline PSA and must be confirmed within 4 weeks. Subjects will complete follow-up within the 9-month duration once PSA response is confirmed per the central lab.

To be evaluable for PSA response, applicable subjects should undergo RT with fields and target volumes adjusted based on presence of PyL-positive prostate bed, pelvic nodal, visceral or limited osseous metastases.

8.6. Change in Management Intent

The intended clinical management plan for a subject will be entered into the eCRF based on the treating investigator's assessment prior to ^{18}F-DCFPyL PET/CT imaging and within 60 days following ^{18}F-DCFPyL PET/CT imaging.

Medical Management Questionnaires (MMQs) will be completed by the treating investigator at two time-points during the study to capture any change in the intended clinical management plan for a subject:

- **Prior to ^{18}F-DCFPyL dosing,** the treating investigator will complete the Pre-PyL MMQ based on baseline clinical information and results from conventional imaging.
- **Post-^{18}F-DCFPyL imaging**, the treating investigator will complete the Post-PyL MMQ based on the additional result from the ^{18}F-DCFPyL PET/CT scan, to assess whether intended change to the initial medical management plan may be warranted due to the PyL finding.

9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

9.1.1. Demographic Information and Medical History

Demographic and baseline information, including date of birth (DOB), race, ethnicity, and height and weight will be collected and recorded in the eCRF.

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, biopsy results, and all past/present therapies.

Other clinically relevant medical history will be recorded 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. All conditions that correspond with the subject's concomitant medications will be recorded in the eCRF.

9.1.2. Vital Signs

Vital sign measurements will include blood pressure (BP) and heart rate (HR). All measurements should be obtained from the subject in the sitting position and measured at two intervals on the day of dosing, including pre- and post-PyL dosing.

9.2. Adverse and Serious Adverse Events

9.2.1. Definition of Adverse Events

9.2.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a research subject administered an investigational product (IP) at any dose, which does not necessarily have a causal relationship with the IP. An AE can therefore be any unfavorable and unintended sign, symptoms or disease temporally associated with the use of the IP, whether or not considered related to the IP.

All AEs (related and unrelated) will be collected after ^{18}F-DCFPyL dosing on Day 1 and again via a safety phone call at 7 (±3) days following ^{18}F-DCFPyL dosing to document possible late-occurring AEs. All AEs must be recorded according to Section 9.4.

9.2.1.2. 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 patient'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.

9.2.2. Overdose and Underdose

For this study, any administered dose of ^{18}F-DCFPyL differing from the prescribed dose of 9 mCi (333 MBq) by more than 20% will be considered a dosing deviation. An overdose is any administered dose greater than 10.8 mCi (400 MBq). Progenics does not recommend specific treatments for an overdose. In the event of an overdose, the subject should be monitored for any AEs for the duration of the safety reporting period. Likewise, an underdose is any administered dose less than 7.2 mCi (266 MBq). The study site should comply with the reporting requirements of their radioactive materials license and 10 CFR Part 35 - Medical Use of Byproduct Material.

9.3. 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 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." If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated."

9.4. Recording Adverse Events

Adverse events spontaneously reported by the 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.

Information about AEs and SAEs will be collected from the first administration of study drug until the follow-up safety phone call. 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, outcome, 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 seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 9.2.1.2. An AE of severe intensity may not be considered serious. Conversely, a serious AE can be of mild or moderate intensity.

9.5. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded at the same interval defined for AE collection as indicated in Section 9.2.1.1. Any SAEs considered at least *possibly related* to the investigational product and discovered by the Investigator at any time *after* the protocol-defined reporting period, should be reported to the Sponsor or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE form, 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 signed and dated follow-up SAE form, within 24 hours of first becoming aware of the additional information.

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

10. STATISTICS

10.1. Sample Size

The primary endpoint is the correct localization rate (CLR) at the subject level, in subjects with positive PyL PET/CT findings, defined as the percentage of subjects with a one-to-one correspondence between localization of at least one lesion identified on ^{18}F-DCFPyL PET/CT imaging and the composite truth standard. The composite truth standard is defined in Section 8.1.

The assumed CLR of ^{18}F-DCFPyL PET/CT imaging is 30%. Based on the variable published experience with ^{68}Ga-PSMA PET/CT and a meta-analysis by Perera *et al*[60], approximately 76% (95% confidence interval [CI], 66-85%) of PSMA scans are positive in patients with suspected recurrence of prostate cancer following initial therapy. Therefore, in subjects with negative or equivocal findings for prostate cancer on baseline conventional imaging, 60% of subjects are conservatively estimated to have PyL PET/CT positive findings. In consideration of the extent of ^{68}Ga-PSMA PET literature and the present study entry criteria, approximately 30% of PSMA PET positive findings may be verified by biopsy/surgery-based histopathology, conventional imaging, or PSA follow-up post-RT.[48,58,61,62] It is therefore assumed that 30% of the positive PyL results in the study will be confirmed by the composite truth standard. If 60% of the study subjects have positive PyL scans, and 30% of these positive diagnostic scans are confirmed by the composite truth standard, the use of the PyL PET/CT will permit the detection/localization of recurrent prostate cancer in approximately 18% of the study population, versus at most 5% that could be identified by conventional imaging alone.

The sample size estimates are based on the positive likelihood ratio (PLR) of CLR to prevalence.

The PLR is estimated as $PLR = (\frac{CLR}{1-CLR})/(\frac{prevalence}{1-prevalence})$.

Conservatively assuming the initial prevalence rate as a population parameter to be 5% by conventional imaging,[42,43] if a CLR of 30% is realized, the positive likelihood ratio is expected to be 8.1,implying a considerable increase in the clinical value of PyL PET/CT to identify prostate cancer.

Using a lower bound for the 95% CI for CLR of 20%, the corresponding lower bound for PLR would be 4.75 based on a normal approximation to the Binomial. This will thus require a total of 81 positive PyL scans, which translates to a total of 134 PyL PET/CT scans or evaluable subjects needed. Accounting for a 30% non-evaluable (including loss to follow-up) rate, approximately 192 subjects will need to undergo PyL PET/CT in the study.

During study enrollment, the rate of positive ^{18}F-DCFPyL PET/CT scans will be calculated periodically to confirm the assumption of 60%. If the observed rate is lower than expected, the sample size may need to be increased.

10.2. Analysis Populations

10.2.1. Safety Population

All subjects who receive any amount of ^{18}F-DCFPyL.

10.2.2. Full Analysis Set (FAS)

All subjects who have received any amount of ^{18}F-DCFPyL and have ^{18}F-DCFPyL PET/CT imaging results.

10.2.3. Per Protocol Set

The per protocol population will consist of the FAS excluding subjects with major protocol violations.

10.3. Missing Data

No imputation of missing data will be applied, with the exception of partial dates for prior treatments or medications.

10.4. Analyses

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

10.4.1. Subject Characteristics

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

Baseline characteristics will be summarized for the Safety Population and the Full Analysis Set.

10.4.2. Efficacy Analyses

Efficacy endpoints will be assessed using the FAS. Continuous monitoring will be performed with respect to the number of subjects evaluable for the primary endpoint. When the required number of subjects with positive ^{18}F-DCFPyL PET/CT scans and information for the composite truth standard are available for calculation of the CLR, subject enrollment and follow-up assessments will conclude, and the study database will be locked for analysis. Any subjects who are undergoing efficacy evaluations who have not contributed endpoint data at the time of database lock will be censored and will be treated as unevaluable for efficacy.

10.4.2.1. Primary Endpoint Analysis

The primary endpoint of the CLR is evaluated in a subset of FAS subjects with at least one positive lesion identified by PyL PET/CT imaging (per local interpretation). The CLR at the subject-level is defined as the percentage of subjects for whom there is a one-to-one correspondence between localization of at least one lesion identified on ^{18}F-DCFPyL PET/CT imaging and the composite truth standard.

The composite truth standard is defined in Section 8.1.

The CLR is computed as 100×TP/(TP+FP); TP = true positives, FP = false positives.

A true positive (TP) result is defined as a subject with both a positive lesion(s) on ^{18}F-DCFPyL PET/CT and a positive result on the composite truth standard:

- Positive finding for prostate cancer of a PyL-suspected lesion according to local histopathology (one confirmed anatomical correlate will suffice to declare the PyL PET/CT a true positive), or
- Positive finding for prostate cancer of a PyL-suspected lesion upon follow-up conventional imaging performed following PyL PET/CT (one confirmed anatomical correlate will suffice to declare the PyL PET/CT a true positive), or
- PSA decreases drop by ≥50% from baseline following RT without concomitant ADT up to 9 months following initiation of such treatment.

False positives will be defined as subjects with positive lesion(s) on PyL PET/CT who have the following negative findings for prostate cancer according to the composite truth standard:

- Negative finding for prostate cancer of a PyL-suspected lesion according to local histopathology, or
- Negative finding for all PyL positive lesion(s) upon follow-up conventional imaging performed following PyL PET/CT (one confirmed anatomical correlate will suffice to declare the PyL PET/CT a true positive), or
- PSA does not drop by ≥50% from baseline following RT (without concomitant ADT) up to 9 months following initiation of such treatment.

The two-sided 95% CI for the CLR will be computed using the normal approximation to the binomial distribution. This analysis will be performed for each of the central imaging core lab

readers. If the lower bound of the 95% CI is >0.2 for two of the three independent imaging reviewers, then the primary endpoint analysis is deemed a success.

10.4.2.2. Secondary Endpoints Analyses

The secondary efficacy endpoint will be generated on the FAS for all subjects regardless of finding(s) on PyL PET/CT imaging, and be analyzed using a two-sided 95% CI presented for each imaging reviewer separately based on a normal approximation to the binomial:

- The percentage of subjects with a change in intended prostate cancer treatment plan from Pre- and Post ^{18}F-DCFPyL PET/CT scan evaluated using a one sample binomial test. A summary of shifts in planned management from Pre- and to Post- ^{18}F-DCFPyL imaging evaluations will also be presented.

10.4.2.3. Exploratory Endpoint Analyses

Exploratory efficacy endpoints will be generated on the FAS for detection rates on the subset of the FAS with at least one positive lesion identified by PyL PET/CT imaging for PPV and false positive scan rate endpoints.

The following endpoints will be analyzed using a two-sided 95% CI presented for each imaging reviewer separately based on a normal approximation to the binomial:

- Detection rates of ^{18}F-DCFPyL PET/CT imaging by lesion locations (i.e., prostatic, pelvic, extra-pelvic)
- The PPV of ^{18}F-DCFPyL PET/CT for (1) prostatic, (2) pelvic, (3) extra-pelvic regions from the composite truth standard in subjects with positive lesion(s) on ^{18}F-DCFPyL PET/CT imaging
- The percentage of subjects with positive ^{18}F-DCFPyL PET/CT scans who have negative findings for prostate cancer (false positive scans) based on the composite truth standard
    - The percentage of false positive scans is defined as (1-CLR)
- The detection rates of ^{18}F-DCFPyL PET/CT imaging as a function of baseline PSA groups

10.4.3. Safety Analyses

All Safety parameters will be presented for the Safety Population.

10.4.3.1. Exposure

Volume administered of ^{18}F-DCFPyL (mL) and activity administered (mCi) will be summarized using the Safety Population.

10.4.3.2. Treatment-Emergent Adverse Events

Treatment-emergent adverse events will be those observed from immediately post-dosing of ^{18}F-DCFPyL on Day 1, through the safety phone call 7 (±3) days post- ^{18}F-DCFPyL dosing for late-occurring TEAEs.

Adverse event verbatim terms will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the start of the study. This version will be used throughout the course of the study. The frequency and percentage of subjects with an adverse event will be summarized by system organ class and preferred term. Adverse events will also be summarized by maximum severity and separately, by highest relationship to treatment.

Serious adverse events, adverse events leading to study discontinuation and adverse events leading to death will be listed.

10.4.3.3. Vital Signs

Changes in vital signs relative to ^{18}F-DCFPyL dosing will be computed as the post-dosing values (1-2 hours post-^{18}F-DCFPyL dosing) minus the pre-dosing value. Observed values and changes, when computed, will be tabulated for each visit using summary statistics.

10.4.3.4. Concomitant Medications and Procedures

Concomitant medications, coded using the current version of the WHO Drug dictionary at the start of the study, will be tabulated. A concomitant medication is a medication administered in the period between the day of ^{18}F-DCFPyL dosing through the Follow-up phone call. Non-concomitant medications (those administered prior to dosing of ^{18}F-DCFPyL) will also be tabulated and considered to be "prior" medications. Concomitant procedures are all procedures performed from the time of ^{18}F-DCFPyL dosing until the follow-up visits are completed. Concomitant procedures will be coded using the same version of MedDRA as for medical history.

11. 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 Injection. 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.

11.1. Study Site Monitoring

Before an investigational site can enter a patient into the study, a representative of the 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.

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

11.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB 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, GCP 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.

12. 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.

12.1. 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 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.

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

The final study protocol, including the final version of the ICF, 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.

12.3. 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 ICF. A copy of the signed ICF must be given to the patient.

12.4. 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 ICF) 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].

12.5. Financial Disclosure

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

13. DATA HANDLING AND RECORDKEEPING

13.1. 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.

13.2. 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 11.2.

13.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of two (2) years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation, or per applicable local regulatory requirement, whichever is longer. 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.

14. 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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