STATISTICAL ANALYSIS PLAN
PHASE II-III

VERSION:
2.0

STUDY DRUG:

^{18}F-DCFPyL Injection (PyL)

PROTOCOL

NUMBER: *PyL-2301*

NCT02981368

STUDY TITLE:

*A Pr**O**spective Phase 2/3 Multi-Center **S**tudy of ^{18}F-DCF**P**yL PET/CT Imaging in Subjects with P**R**ostate Cancer: **E**xamination of Diagnostic Accurac**Y** (OSPREY)*

SPONSOR:

Progenics Pharmaceuticals, Inc.

One World Trade Center

47th Floor, Suite J

New York, NY 10007

646-975-2500

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
^{18}F	fluorine 18
ADT	androgen deprivation therapy
AE	adverse event
ATC	anatomical therapeutic classification
AUC	area under the curve
BN	bone
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed concentration
CL	clearance
cm	centimeter
CPM	counts per minute
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated Glomerular filtration rate
ePLND	Extended lymph node dissection in prostate cancer
FN	false negative
FP	false positive
HR	heart rate
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
I(p)	total positive imaging
I(n)	total negative imaging
Kg/m^2	kilograms per metered squared
LLN	lower limit of normal
LN	lymph node
MBq	Megabecquerel
mCi	millicurie
MDRD	Modification of diet in renal disease study

Table 1: List of Abbreviations

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MRI	magnetic resonance imaging
MRT	mean residence time
NC	North Carolina
ng/mL	nanogram/milliliter
NPV	negative predictive value
PET/CT	positron emission tomography/computed tomography
PK	pharmacokinetics
PPV	positive predictive value
PSA	prostate specific antigen
PSMA	Prostate specific membrane antigen
PT	preferred term
R(n)	total negative histopathology
R(p)	total positive histopathology
RP	radical prostatectomy
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SOC	system organ class
ST	Soft tissue
SUV_{max}	maximum standardized uptake value
SUV_{mean}	Mean standardized update value
SUV_{peak}	peak standardized uptake value
SUV_{r}	ratio to reference tissue standardized uptake value
TEAE	treatment-emergent adverse event
$T_{1/2}$	half life
$T_{1/2alpha}$	alpha phase distributive half life
$T_{1/2beta}$	beta phase elimination help life

Table 1: List of Abbreviations

Abbreviation	Term
$T_{1/2elim}$	elimination half life
T_{max}	time to maximum concentration
TN	true negative
TOA	time of administration
TP	true positive
ULN	Upper limit of normal
USA	United States of America
V_{ss}	steady state volume of distribution
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

The statistical analysis plan (SAP) is based on:

- Protocol amendment 2 dated November 6, 2017,
- ICH guidelines E6[1] and E9[2].

The purpose of this document is to provide details about study populations, how variables will be derived, how missing data will be handled as well as details about statistical methods to be used to analyze the safety and efficacy data from Study PyL-2301.

The list of tables, listings and their shells are guidelines which may be refined to facilitate programming. Such changes will not be documented in an amendment to this document. However, any changes to populations, endpoints or analysis methods will be documented in a SAP amendment and will be noted in the clinical study report, as relevant.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. 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 subjects with high risk prostate cancer (cohort A).

3.1.2. 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, bio-distribution and excretion of ^{18}F-DCFPyL

3.1.3. 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 extra-prostatic 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 plan
5. To determine PPV of ^{18}F-DCFPyL PET/CT imaging for lesions detected by PET that are outside the planned surgical template or biopsy site

3.2. Efficacy Endpoints

3.2.1. Primary Efficacy 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 in 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 in Cohort A

3.2.2 Secondary Efficacy Endpoints

1. Sensitivity of ^{18}F-DCFPyL PET/CT imaging to detect prostate cancer within sites of metastasis or local recurrence relative to histopathology in Cohorts B
2. Comparison of detection rates for lesion counts overall and by location (i.e., bone, lymph nodes, soft tissue, prostate gland) between ^{18}F-DCFPyL PET/CT and conventional imaging in Cohorts A and B combined
3. PPV of ^{18}F-DCFPyL PET/CT imaging to predict prostate cancer within the prostate gland and lymph nodes in Cohort A
4. NPV of ^{18}F-DCFPyL PET/CT imaging to predict the absence of prostate cancer within the prostate gland and lymph nodes in Cohort A
5. PPV of ^{18}F-DCFPyL PET/CT imaging to predict prostate cancer within sites of local recurrence and other metastatic lesions in Cohort B
6. Pharmacokinetic parameters derived from blood samples [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)

3.2.3 Exploratory Efficacy Endpoints

1. ^{18}F-DCFPyL uptake in different lesion locations as defined by SUV_{peak}, SUV_{max}, and SUV_r results derived from central readers for cohorts A and B combined and compared between histology outcomes
2. To assess the relationship between SUV_{peak}, SUV_{max}, volume, and SUVr and Gleason Score at time of radical prostatectomy, baseline PSA, and testosterone levels for both cohorts
3. Sensitivity of ^{18}F-DCFPyL PET/CT imaging within the prostate gland relative to histopathology in Cohort A
4. Specificity of ^{18}F-DCFPyL PET/CT imaging within the prostate gland relative to histopathology in Cohort A
5. Changes to clinical management 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 (Cohort A only)
6. PPV of ^{18}F-DCFPyL PET/CT imaging in subjects with corresponding histopathology for subjects who had a change in the planned protocol procedure (Both Cohorts combined)

3.3. Safety Endpoints

1. Treatment-emergent adverse events (TEAEs) and SAEs
2. Change from baseline in clinical laboratory parameters
3. Change from baseline in ECGs
4. Change from baseline in vital signs
5. Concomitant medication use

4. STUDY DESIGN

4.1. Summary of 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 high risk prostate cancer who were 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) who were biopsied if a positive lesion was found on the ^{18}F-DCFPyL PET/CT scan. The physician has the option to change the planned protocol specified procedure (i.e., RP ePLND for Cohort A subjects and Biopsy for Cohort B subjects) for the subjects based on the ^{18}F-DCFPyL PET/CT scan. The details of these changes will be collected on the CRF, and these subjects obviating the planned procedure will not be included in any of the primary or secondary endpoints.

Eligible subjects will be enrolled in a non-randomized, sequential manner, with competitive enrollment between study sites. Ten (10) study sites will be used in the U.S. and Canada.

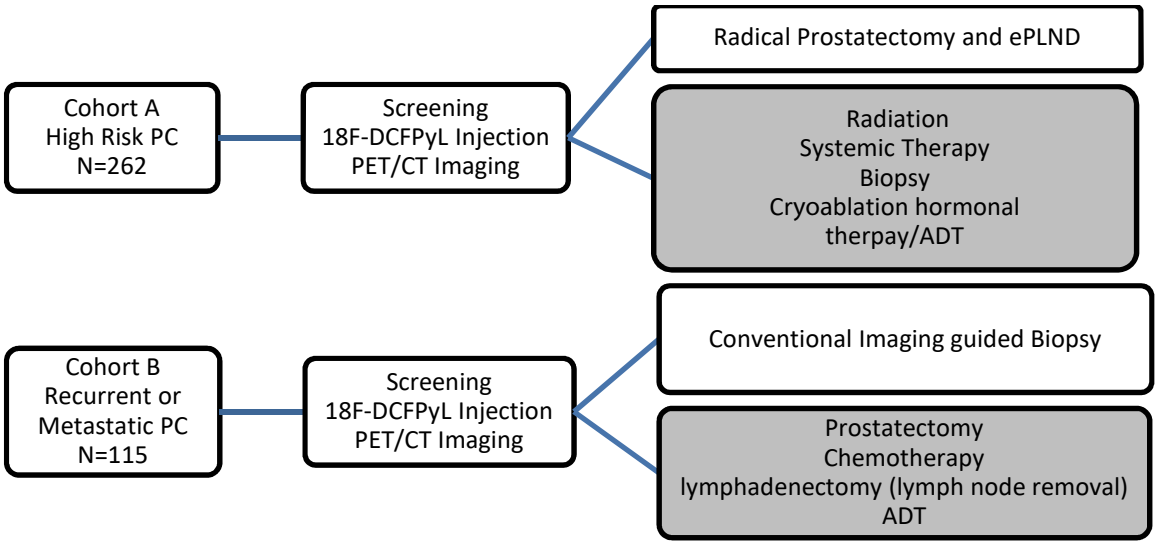
Diagnostic performance characteristics of ^{18}F-DCFPyL PET/CT imaging will be evaluated using histopathology as the truth standard. Three independent readers from a central imaging core lab will be given access to ^{18}F-DCFPyL PET/CT imaging, conventional imaging, and biopsy-guided imaging. The central readers will be blinded to all other clinical information (i.e. pathology data) and radiology assessments. Likewise, local pathologists who generate the histopathology results for the primary endpoint are blinded to all imaging results.

A change in clinical management questionnaire will be filled out by an independent urologist who is not otherwise a participant of the study. To maintain the blind for imaging, a statistician who is independent from the PyL study team will generate subject listings. A combination of imaging and clinical data will then be posted to a share point site where the independent urologist will review these data and fill out the questionnaire based on the results he sees prior to PyL imaging and then again after PyL imaging. To keep things simple, only imaging data from reviewer 1 will be presented for this assessment to be performed.

4.2. Definition of Study Drugs and Treatment Follow-up

All subjects will be administered 9 ± 1 mCi (333 ± 37 MBq) ^{18}F-DCFPyL injection followed by PET/CT imaging and either a biopsy or prostatectomy and lymphadenectomy as illustrated in the white boxes in Figure 1. These are the protocol's planned procedures. If a Physician decides to change these planned procedures after PET/CT imaging is obtained, subjects in Cohort A would not have surgery and subjects in Cohort B would not have a conventional imaging guided biopsy. These changes in planned protocol procedures are listed in the shaded boxes below. This should be a small number of subjects who will not be included in the primary analysis of the primary endpoint or any of the secondary endpoints.

Figure 1: Study Schema



If the subject did not want to go through with this planned procedure or withdrew from the study then this would not constitute a change in planned protocol procedure. If the planned procedure was intended but could not be completed, then this is also not a change in planned procedure.

4.3. Sample Size

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 the evaluable set of subjects in Cohort A with metastatic disease. 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 leading to overall success of the primary endpoint. The null hypotheses will be tested in the following order:

1. Specificity of ^{18}F-DCFPyL PET 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_{01}: $\pi_{Se} = 0.40$ versus H_{11}: $\pi_{Se} \neq 0.40$

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

A total of 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[3].

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

where 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 subjects are needed. Assuming a 10% drop out or non-evaluable rate increases the required number of subjects in Cohort A to 262.

The type I error rate will be preserved at 5% by requiring that both null hypotheses be rejected 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 the 0.05 level of significance per a fixed sequential method. If the first hypothesis fails to be rejected, no further testing will be conducted.

No formal power calculations will be performed for Cohort B since it is not a primary endpoint. Approximately 115 subjects will be dosed in this cohort.

4.4. Randomization

This study is not randomized. One treatment will be administered.

4.5. Clinical Assessments

See Table 2 for the schedule of study assessments.

Table 2: 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)	X			
Medical History	X			
Prior Cancer Medications & Treatments	X			
Clinical Labs (hematology, chemistry)	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 ECG		X (pre-dosing)	X (pre-imaging)	
^{18}F-DCFPyL Administration		X		
Whole Body PET/CT			X	

Table 2: 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
Adverse Events		X		X[5]
Concomitant Medications	X	X		X
Conventional Imaging (CT or MRI, bone scan)	X[2]			
Surgery or Image-Guided Biopsy				X[3,6]
Subset of Cohort A or B at Johns Hopkins University only for PK Analysis				
Blood Collection		X[4] (9 collections)		
Urine Collection		X[4] (3 collections)		
Whole Body PET/CT			X[4] (3 scans)	

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. If Na-^{18}F-PET bone scans conducted at screening must be at least 10 hours prior to dosing.

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 Analysis should occur immediately following last sample collected.

5 A safety phone call will also occur 7(±3) days post dosing [if surgery, biopsy or a change in planned protocol procedure has not yet occurred] and 21(±7) days post biopsy for just the subjects who had a conventional image guided biopsy in Cohort B.

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).

4.6. Interim Analyses

No interim analysis is planned for this study.

4.7. Final Analyses

The final analysis will be conducted after the database is locked.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Subject Data Listing Considerations

Adverse event and medical history verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 4.0. Medications will be coded using the World Health Organization Drug Dictionary (WHODDE) from December 2016.

Summary tables and listings will include the following information: dataset(s) used in table production, date of data extract, date of output generation, the SAS program name and location (directory path), page x of y numbering. Adverse event and medical history summaries will indicate the MedDRA version; prior and concomitant medication summaries will indicate the WHODD version.

Summary tables for demographics and baseline characteristics, medical history, exposure, concomitant medications, and safety will include the following columns: Cohort A, Cohort B, overall (Cohorts A and B combined). Efficacy tables will be produced by cohort.

5.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Statistical analyses will be performed, and datasets and tables will be generated using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

5.3. Data Presentation Conventions

Continuous data will be summarized using descriptive statistics [i.e., N, arithmetic mean, standard deviation (SD), median, minimum, and maximum]. The minimum and maximum will be displayed to the same level of precision as collected data; mean and median will be displayed to one level of precision greater than the data collected; SD will be displayed to two levels of precision greater than the data collected. Categorical data will be described using frequencies and percentages. A row for missing values will be included, when applicable. P-values will be presented at four decimal places.

Dates will be presented in DDMMMYY format and times will be presented as HH:MM using a 24-hour clock.

In tables and listings, columns of data will be decimal aligned.

5.4. Analysis Populations

5.4.1. Consented Set

All subjects who sign an informed consent document will be included in the consented set.

5.4.2. Safety Set

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

5.4.3. Evaluable Set

Evaluable subjects in Cohort A are those who were dosed, had a prostatectomy or lymphadenectomy, and provided a ^{18}F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive or negative).

Evaluable subjects in Cohort B are those who were dosed, received a conventional image guided biopsy, and provided a ^{18}F-DCFPyL PET image result (positive or negative) and a corresponding histopathology result (positive for prostate cancer or negative), along with a conventional image that confirms the location of the histopathology sample.

5.4.4. Change in Planned Protocol Procedure Set

The change in planned protocol procedure set includes dosed subjects in Cohort A who did not have a prostatectomy and lymphadenectomy due to change of planned management, and subjects in Cohort B who did not have conventional guided biopsy due to change of planned management. See figure 1 above for definition of change in planned management.

5.4.5. Per Protocol Set

The Per-protocol set is defined as subjects in the Evaluable set without any major protocol deviations. Major protocol deviations will be identified prior to database lock and analysis.

5.4.6. PK Blood Set

Subjects who provide at least six of the nine scheduled blood samples.

5.4.7. PK Urine Set

Subjects who provided at least two of the three scheduled urine samples.

5.5. Derived and Transformed Data

5.5.1. Baseline Definition

Baseline will be the latest pre-dose value.

5.5.2. Baseline Age

Age is computed in the database as the number of full year increments from date of birth to informed consent date.

5.5.3. Study Day

Study day will be computed as the date of assessment minus the Dosing date (plus one if the assessment date is on or after the dose date).

5.5.4. Change and Percent Change from Baseline

Change from baseline will be computed as any post baseline follow-up value minus the baseline value.

Percent change from baseline will be computed as 100 times the (post-baseline value minus the baseline value) divided by the baseline value. If the baseline value or the post-baseline value is missing, change from baseline and percent change from baseline will be missing.

5.5.5. Prior and Concomitant Medications

Prior medications are those administered prior to ^{18}F-DCFPyL administration date; concomitant medications are those administered from ^{18}F-DCFPyL administration through last study visit. If the concomitant medication does not have a full date then the algorithm in Section 5.6.2 will be used to determine if it is a pre- or post-dose medication.

5.5.6. Treatment-Emergent Adverse Events

Treatment emergent AEs are defined for all subjects as AEs occurring from the day of, but after ^{18}F-DCFPyL administration through the date prior to prostatectomy, lymphadenectomy, or change in planned procedure for subjects who underwent a procedure. For subjects who did not receive a procedure, TEAEs are collected up to10 days after drug administration. For subjects in Cohort B who had a conventional imaging guided biopsy only, treatment emergent is defined as AEs occurring from the day of ^{18}F-DCFPyL administration through 28 days post biopsy.

5.5.7. Sensitivity, Specificity, PPV, and NPV

Sensitivity, specificity, PPV and NPV will be defined based on a ^{18}F-DCFPyL image result (positive or negative) and a histopathology result (positive or negative).

Table 3: Classification of ^{18}F-DCFPyL Imaging Result and Histopathology Result

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

TP=true positive; FP=false positive; FN=false negative; TN=true negative.
R(p) and R(n) denote the number of subjects with positive and negative histopathology results, respectively.
I(p) and I(n) denote the number of subjects with positive and negative ^{18}F-DCFPyL images, respectively.
N indicates the number of subjects
*positive histology 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).

5.5.7.1. Primary Endpoints and Pelvic Lymph Nodes

The primary endpoints of sensitivity and specificity are defined from lymph node imaging results and corresponding pelvic lymph node histology. For an imaging result to be deemed positive for this endpoint, the tissue must have first been removed from that corresponding area. This ensures that an imaging result has the ability to align with the results achieved from pathology. This will be applied to Cohort A subjects only.

PPV and NPV will also be calculated as secondary endpoints from the pelvic lymph nodes. The same definitions used below will apply.

Criteria for Positive PyL Imaging Result	**Criteria for Lymph Node Dissection and Positive Histology**
If Right or Left Pelvic Lymph Nodes Minimum Template = Positive and • Tissue was removed from left template and total left nodes removed ≥1 and Template Left Pelvic LN Lesion Count ≥1 or • Tissue was removed from right template and total right nodes removed ≥1 and Template Right Pelvic LN Lesion Count ≥1 or Tissue was removed from Pre-sacral nodes and total pre-sacral nodes removed ≥1 and Pre-Sacral Pelvic LN Lesion Count ≥ 1 or Tissue was removed from Other lymph nodes and Total nodes removed >=1 and Other Pelvic LN Lesion Count ≥ 1 or	≥1 positive lymph node on right template if Template Right Pelvic LN Lesion Count from imaging is ≥0 or ≥1 positive lymph nodes on left template if Template Left Pelvic LN Lesion Count from imaging is ≥0 or ≥1 positive lymph nodes on pre-sacral nodes if Pre-Sacral Pelvic LN Lesion Count from imaging is ≥0 or ≥1positive lymph nodes on other pelvic lymph nodes if Other Pelvic Lymph Node Count from imaging is ≥0

If tissue was removed from right template and total right nodes removed ≥1 and resection included tissue along the external iliac artery and Right pelvic lymph node external iliac artery= positive or If tissue was removed from left template and total left nodes removed ≥1 and resection included tissue along the external iliac artery and left pelvic lymph node external iliac artery= positive or If tissue was removed from right template and total right nodes removed ≥1 and resection included tissue along the common iliac vein and Right pelvic lymph node common iliac vein= positive or If tissue was removed from left template and total left nodes removed ≥1 and resection included tissue along the common iliac vein and left pelvic lymph node common iliac vein= positive or If tissue was removed from right template and total right nodes removed ≥1 and resection included tissue along the common iliac artery and Right pelvic lymph node common iliac artery= positive or If tissue was removed from left template and total left nodes removed ≥1and resection included tissue along the common iliac artery and left pelvic lymph node common iliac artery= positive	If Template Right Pelvic LN Lesion Count from imaging is ≥0 and Total number of positive lymph nodes from Right Template ≥1 or If Template Left Pelvic LN Lesion Count from imaging is ≥0 and Total number of positive lymph nodes from Left Template ≥1

If any of the above criteria are met for imaging then PyL Imaging Result=Positive. If Cohort =A and lymphadenectomy was performed, and lesion counts from imaging results are available for at least one location (right, left, pre-sacral or other) but the above criteria are not met for imaging, then PyL Imaging Results = Negative.

If the above criteria for histology are met then Histology is positive. If all available positive lymph nodes=0 where the corresponding lesion count from imaging≥0 then Histology is negative.

If the lesion counts from all 4 locations (right, left, pre-sacral, and other lymph nodes) are not evaluable on imaging or tissue is not removed from all 4 locations then this endpoint will be missing.

5.5.7.2. Biopsy

Sensitivity and PPV are defined from imaging results in subjects undergoing a biopsy confirmed by conventional imaging and histology obtained from this biopsy. This will be performed for Cohort B only.

Criteria for Positive PyL Imaging Result	Criteria for Biopsy and Positive Histology
Biopsied Lesion consistent with PSMA Positive uptake on the ^{18}F-DCFPyL PET/CT = yes	Pathology result=Positive for prostate cancer

If Cohort =B, imaging and histology are obtained for the biopsy, and the above criteria are not met (Biopsied Lesion consistent with PSMA Positive uptake on the ^{18}F-DCFPyL PET/CT = no or pathology result = negative) then results = Negative for each respective endpoint.

5.5.7.3. Prostate Gland

Sensitivity, specificity, PPV and NPV will be calculated from imaging and histology results from the prostate gland. This will be performed for subjects in Cohort A only.

Criteria for Positive PyL Imaging Result	Criteria for Positive Histology
For category = PYL and Prostate gland right lesion count ≥ 1 or Prostate gland left lesion count ≥ 1	If Prostate gland right lesion count ≥0 from imaging and Adenocarcinoma is present at right side of prostate or Prostate gland left lesion count ≥0 from imaging and Adenocarcinoma is present at left side of prostate

If Cohort =A and Adenocarcinoma results are not missing for the right or left side of the prostate and the above criteria is not met, then result = Negative.

If imaging results are both not evaluable or the presence of adenocarcinoma is missing from both the left and right side of the prostate then this endpoint is missing.

5.5.7.4. PPV for Changes in Planned Treatment

PPV will be calculated from imaging and histology results for the subset of subjects who had a change in the planned protocol procedure. Only a subset of these subjects may have tissue available for PPV.

Criteria for Positive PyL Imaging Result	Criteria for Procedure and Positive Histology

If subject in Cohort A and category=PYL and Is the 18F-DCFPyL PET/CT scan consistent with PSMA Positive cancer uptake = yes and Location of lesion count from imaging = location of lesion from histology and Lesion count for location >=1 from imaging	If Cohort A and prostatectomy and lymphadenectomy performed=no and Reason= Other, unscheduled Biopsy='Yes' and Pathology result=Positive for prostate cancer
If Cohort B and category = PYL and Prostate gland right lesion count ≥ 1 or Prostate gland left lesion count ≥ 1	If Cohort B and Biopsy performed =no and Adenocarcinoma present at right or left side of prostate = yes
If Cohort B and category = PYL and positive imaging criteria from Section 5.5.7.1 is met.	If cohort B and biopsy performed = no and ≥1 positive lymph node on right or left template, pre-sacral nodes, or other pelvic lymph nodes

The denominator of the above subset is the subset of subjects who had a change in the planned protocol procedure defined in Figure 1 and who had both imaging and histology results.

If imaging results are not evaluable then this endpoint is missing.

5.5.8. Lesions Per Subject

The number of lesions detected on imaging categorized as bone, lymph nodes, soft tissue, and the prostate gland will be determined by each of the central imaging core lab independent readers. The sum of lesions per subject per tissue type and overall will be computed for each subject based on each reader's lesion count. This will be calculated from the ^{18}F-DCFPyL PET/CT scan results as well as the conventional imaging results.

Bone	Soft Tissue	Lymph nodes	Prostate Gland
BN Skull	ST Brain	LN Cervical	ST Prostate Gland Left
BN Thorax	ST Neck	LN Supraclavicular	ST Prostate Gland Right
BN Spine	ST Lungs	LN Axillary	
BN Pelvis	ST Esophageal	LN Mediastinal	
BN Extremities	ST Liver	LN Hilar	
	ST Gall Bladder	LN Mesenteric	
	ST Spleen	LN Elbow	
	ST Pancreas	LN Popliteal	
	ST Adrenal	LN Peri-aortic/para-aortic	
	ST Kidney	LN Other, Non-Pelvic	
	ST Bladder	PLN Template Right	
	ST Prostate Bed	PLN Template Left	
	ST Seminal Vesicle	PLN Pre-Sacral	
	ST Skin	PLN Other, Pelvic	
	ST Muscle		
	ST Other		

5.5.9. Visit Windows

Data will be analyzed according to the nominal time points. Visit windows will not be used.

5.5.10. Decay Corrected Dose at Time of Administration

The calculations in this section will need to be performed for the pre- and post- injection values for ^{18}F-DCFPyL administration as well as pre- and post- injection from the Syringe to the flask for reference values.

If a decay correction was performed for the pre-or post- dose values then Correction Factor =1. Otherwise:

Correction Factor = $e^{(\ln(2)*(pre\ or\ post\ injection\ time(min)-injection\ time\ (min)))/110\ min}$

where the above formula will be calculated for each of the following pre and post injection times:
- pre-dose
- post dose
- syringe prior to flask
- syringe post flask
- start of measurement times with each PK period

Convert all pre- and post- injection amounts to mCi: 37MBq = 1mCi

If there was no post decay correction then:

Decay Corrected Dose at time of Administration = (pre injection amount (mCi)*Correction Factor Pre Dose)- $\frac{Post\ injection\ amount\ (mCi)}{Correction\ Factor\ Post\ Dose}$

If there was a post decay correction then:

Decay Corrected Dose at time of Administration(mCi) = (pre injection amount(mCi) – post injection amount(mCi))

Calculate decay corrected doses at time of administration in both mCi for all subjects and MBq for all subjects.

The Decay corrected pre-injection Reference Standard of syringe prior to injection into flask = amount (µCi) in syringe prior to injection into flask*Correction Factor of syringe prior to flask.

The Decay corrected post-injection Reference Standard of syringe after injection into flask = amount (µCi) in syringe after injection into flask*Correction Factor of syringe after flask.

The decay corrected reference standards are only needed in µCi.

5.5.11. Lesion location defined from SUV values

There are three SUV values collected: SUV_{max}, SUV_{peak} and SUV_{mean}. There are four locations that each of these SUV values could be present in: Bone, Soft tissue, prostate, and lymph nodes ('prostate gland right' and 'prostate gland left' were defined as a separate location from soft

tissue) as defined in Section 5.5.8. There are three reference values per subject at the following locations: Aorta, Liver and Muscle. For each tumor location that is not a reference location, SUV_R will be calculated against each reference as follows:

$$SUV_R = \frac{SUV_{MAX\_Tumor}}{SUV_{MEAN\_Reference}}$$

Some subjects may have multiple SUV values within each location. These results will be averaged to derive one result per location and since there results should be similar per reviewer, only results for reviewer 1 will be used in any analyses. Subjects in Cohort B may have both a biopsied lesion and a tissue lesion within the same location. These SUV values should be summarized separately.

5.5.12. Change in Clinical Management Plan from Questionnaire

A change in the Clinical Management plan from the pre-PyL scan assessment to the post-PyL scan assessment will be defined from any of the following questions:

- If there is a change in planned diagnostic biopsy from pre-PyL to post-PyL
- If there is a change in planned surgery from pre-PyL to post-PyL
- If type of surgery planned pre-PyL does not match post-PyL
- If type of planned chemotherapy changes from pre-PyL to post-PyL
- If there is a change in planned other immunotherapy/investigational therapy from pre-PyL to post-PyL
- If planned radiation therapy changed from pre-PyL to post-PyL
- If chemotherapy plan changed from pre-PyL to post-PyL
- If hormonal/ADT plan changed from pre-PyL to post-PyL
- If there is a change in other therapy/intervention from pre-PyL to post-PyL

An overall change score will be calculated as well as a change in each of the above criteria alone.

5.5.13. PSA groups

PSA will be categorized into the following groups:

<0.2 ng/mL
0.2 to <4.0 ng/mL
4 to <20.0 ng/mL
20.0 to <50.0 ng/mL
≥50 ng/mL

5.5.14. Gleason Scores

The Gleason score will be derived by concatenating the primary Gleason grade to the secondary Gleason grade, separated by a plus sign (e.g., 3+4). The total Gleason score will be computed as the sum of the primary and secondary Gleason grades (7 in the example of 3+4 provided here).

Gleason Score from prostatectomy will be categorized into the following groups as shown in the table based on the sum of primary and secondary Gleason Grades:

Primary Gleason Grade	Secondary Gleason Grade	Total
3	3	≤ 6
3	4	7
4	3	7
4	4	8
4	5	9
5	5	10

5.5.15. Prior Prostate Cancer History and Therapies

If any of the follow variables have partial dates where only month and year are present, then months will be calculated as ((dose year - parameter year) x12) + ((dose month-parameter month) +1). Otherwise, with full dates, the calculation would be as follows:

Months since last prostate cancer staging = (Dose date – prior prostate cancer staging date)/30.4.

Months from Prior Therapy to Dose = $(Dose\ Date - Prior\ prostate\ Therapy\ stop\ date)/30.4$

Months from Prior Radiation to Dose= $(Dose\ Date - Prior\ radiation\ Therapy\ stop\ date)/30.4$

Months from Prior Surgery to Dose = $(Dose\ Date - Prior\ prostate\ surgery\ date)/30.4$

Months from Staging to Dose= (Dose Date – Primary tumor staging date)/30.4

Months since last Prior Therapy to Dose = (Dose Date – Prior therapy date)/30.4.

Full dates must be present for duration variables below:

Duration of Prior Therapy (days) = (Prior Prostate Therapy stop date – Prior prostate therapy start date) +1.

Duration of Prior Radiation Therapy (days) = (Prior Radiation Therapy stop date – Prior Radiation therapy start date) +1

5.5.16. Estimate GFR

Estimate GFR (eGFR) will be calculated using the Modification of Diet in Renal Disease (MDRD) Equation[4]:

eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr})^{-1.154}$ × (Age in years)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

Where Scr= Serum creatinine (mg/dL)

5.5.17. Renal impairment

If Estimated GFR ≥90 then Normal (no impairment), otherwise if 0≤eGFR<90 then Abnormal.

5.5.18. Laboratory Parameter Unit Conversions

Lab Parameter	Original Unit	Conversion Factor (multiply)	Final SI Unit
ALT, Alkaline Phosphatase	U/L	0.0167	Ukat/L
Albumin, Total Protein, hemoglobin	g/dL	10	g/L
BUN	mg/dL	0.357	mmol/L
Calcium	mg/dL	0.25	mmol/L
Chloride, Potassium, Sodium	mEq/L	1	mmol/L
Creatinine	mg/dL	88.4	umol/L
Glucose	mg/dL	0.0555	mmol/L
Total Bilirubin	mg/dL	17.104	umol/L
Total Testosterone	ng/dL	0.0347	nmol/L
Total Testosterone	ng/mL	3.4672	nmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Hematocrit	%	0.01	L/L
Basophils, Eosinophils, lymphocytes, monocytes, neutrophils, platelets, WBC count	k/cumm	1	10^9/L
Basophils, Eosinophils, lymphocytes, monocytes, neutrophils, platelets, WBC count	k/μL	1	10^9/L
Basophils, Eosinophils, lymphocytes, monocytes, neutrophils, platelets, WBC count	10^3/μL	1	10^9/L
Basophils, Eosinophils, lymphocytes, monocytes, neutrophils, platelets, WBC count	10^9/L	1	10^9/L

Basophils, Eosinophils, lymphocytes, monocytes, neutrophils, platelets, WBC count	k/mcl	1	10^9/L
RBC Count	m/mcl	1	10^{12}/L
RBC Count	m/μL	1	10^{12}/L
RBC Count	mil/cumm	1	10^{12}/L
RBC Count	10^{12}/L	1	10^{12}/L
RBC Count	10^{12}/L	1	10^{12}/L
RBC Count	10^6/μL	1	10^{12}/L
PSA	ng/mL	1	ug/L

5.6. Handling of Missing Data

5.6.1. Missing Efficacy Endpoints

No imputation methods will be employed.

5.6.2. Missing Start and Stop Dates for Concomitant Medication

Partial or missing medication start, and end dates will be categorized as occurring prior to or after dose using the following logic. If a medication categorized as post-dose had a start date< dose date or a start year <dose year or a start year=dose year and start month<dose month then it will be summarized as both a pre- and post- medication.

Start Date	Stop Date	Category
< dose date or Year< dose year or year= dose year and month< dose month or year=dose year or date=missing	date< dose date or year<dose year or year=dose year and month<dose month	Pre-dose
< dose date or Year< dose year or year= dose year and month< dose month	Missing or date< dose date or year<dose year or year=dose year and month<dose month or year=dose year	Pre-Dose
Year = dose year and month = dose month and day is missing	Year = dose year and month < dose month	Pre-dose
>dose date or year=dose year and month≥ dose month	missing	Post Dose
>dose date or year=dose year and month> dose month		Post Dose
	≥ dose date or year>dose year or year=dose year and month ≥ dose month	Post Dose
Date<dose date or year ≤ dose year and month≤dose month	Year=dose year and month=dose month	Post Dose
Missing	missing	Post Dose
< dose date or Year< dose year or year= dose year and month< dose month	≥ dose date or year>dose year or year=dose year and month ≥ dose month	Pre and Post Dose

6. STUDY POPULATION

6.1. Disposition

Subject disposition will display the number of consented subjects and the percentage of them who failed screening. The number of subjects in the safety analysis set as well as the number and percentage of subjects in the evaluable set, per-protocol set, change in planned protocol procedure set, and PK sets will also be summarized. The number and percentage of subjects who completed or discontinued from the study with the reason for discontinuation, will be tabulated. All percentages for discontinuation reasons will be based on the number of subjects in the safety population.

6.2. Protocol Deviations

Protocol deviations will be summarized in the clinical study report based on the protocol deviation log.

Protocol deviations will be listed, including their classification as major or minor for the Safety Set.

6.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics: age at informed consent in years, categorical age (<65 years, ≥65 years), race, ethnicity, height in cm, weight in kg, and BMI in kg/m^2 will be summarized by cohort for the safety set, the evaluable set, and the per protocol set.

6.4. Medical History, including Prostate Cancer History

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT) using frequencies and percentages.

Prior prostate cancer history will also be summarized using summary statistics for months since most recent prostate cancer staging, PSA (ng/mL) and testosterone (ng/dL). Frequencies and percentages will be presented for whether PSA results were captured within 30 days from Baseline, PSA groups, primary Gleason grade, secondary Gleason grade, Gleason total score, primary tumor stage (T), regional lymph node stage (N), distant metastasis stage (M) and renal impairment status.

Medical history and prostate cancer history will be presented for the safety set, the evaluable set and the per-protocol set.

6.5. Prior Prostate Cancer Therapies and Surgeries

For prior prostate cancer therapies, each line of therapy is captured into a group ranging from A-O, where A is the first line of therapy and O is the last line of therapy. The drugs within each are collected. Prior to locking the database, these drugs will be categorized into groups. An additional categorization will also be performed to show types of prostate cancer therapies. These therapies will be summarized overall for the drugs within the different lines of therapies. The number of therapy regimens received, and types of prostate cancer therapies will be summarized.

Radiation therapy will be presented to show whether it was prostate related or not, and radiated site.

Months since last reported surgery will also be summarized. Surgeries will also be presented by system organ class and preferred term.

All prior prostate cancer therapies and surgeries will be presented for the safety set, the evaluable set and the per protocol set.

6.6. Prior Medication History and Medications Present at Entry

Prior medications will be summarized by ATC4 class and generic name using frequencies and percentages. Prior medications will also be listed.

Prior medication history will be presented for the safety set, the evaluable set and the per protocol set.

6.7. Conventional Imaging at Baseline

Type of bone scans, bone scans obtained within 10 hours of dosing, MRI/CT performed, and type of MRI/CT will be summarized by the safety set, the evaluable set and the per protocol set.

7. EFFICACY

7.1. General Considerations

Statistical tests and their corresponding confidence intervals will be two-sided at the 0.05 significance level.

The estimation of sensitivity and specificity rely on the central imaging core lab independent readers. Each reader's assessments will be summarized separately.

7.2. Testing Statistical Assumptions Including Comparability at Baseline

7.2.1. Test of Proportions

The assumption underlying the normal approximation to the binomial distribution, used in the computation of confidence intervals for sensitivity, specificity, PPV, and NPV, is that the sample size is such that $np>5$ and $n(1-p)>5$, where n is the sample size and p is the binomial probability. It is expected that the sample size for each statistic will be sufficient to meet this assumption. In the event that the sample size is not sufficient, Agresti-Coull exact tests will be used. As there is only one treatment in this study, there will be no testing of baseline comparability.

7.2.2. Test of means

The assumption of normality of the data may be violated when testing for differences in means. If data fail the Shapiro-Wilk test for normality within each group, then a Wilcoxon rank sum test will be used for the comparison of 2 groups and a Kruskal-Wallis test for comparison of 3 groups to test for differences in the distribution between groups. For 2 group comparisons, an exact 95% confidence interval will be generated for the difference scores. For a 1-way repeated

measures ANOVA, if the assumption of normality is not met then a Friedman test will be performed.

7.3. Statement of the Null and Alternate Hypotheses

The null and alternative hypotheses are stated in Section 4.3.

7.4. Subgroup Analyses

No subgroup analyses are planned, but they may be examined for exploratory purposes.

7.5. Multiple Comparisons and Multiplicity

Within Cohort A, the type I error rate 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. In addition, the three readers from the central imaging core laboratory are independent and requiring that the same 2 of 3 readers agree about sensitivity and specificity (Cohort A) will control for type I error.

7.6. Analysis of the Primary Efficacy Endpoint

7.6.1. Primary Efficacy Analysis of Primary Endpoints

The primary analysis for subjects 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 assessed on the subject level (one overall outcome per subject) in the *evaluable set*. If the *per protocol* set exists, then this analysis will be performed on the *per protocol* set as a supplemental analysis. The normal approximation to the binomial distribution is planned assuming the assumptions have been met (See Section 7.2). Sensitivity and specificity will be computed for each of three central imaging core lab independent PET/CT readers.

The null hypothesis for specificity will be rejected if the lower limit of the 95% CI exceeds 80% for at least two of the three independent central PET/CT 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 the 95% CI exceeds 40% for the same two readers who rejected the null hypothesis for specificity.

7.6.2. Sensitivity Analyses of the Primary Endpoints

A sensitivity analysis of the primary endpoint will be performed allowing any 2 of the 3 central PET/CT readers to reject the null hypothesis for sensitivity only after specificity has been deemed a success. This analysis will require agreement of at least 2 readers, but they do not need to be 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 sets.

7.7. Analysis of Secondary Efficacy Endpoints

Analysis of secondary efficacy endpoints will be conducted regardless of the outcomes of the primary analyses. Diagnostic testing and imaging detection rates will be analyzed for the evaluable set. The PK parameters will be summarized for the PK blood set.

7.7.1. NPV and PPV in Cohort A

Point estimates and two-sided 95% CIs for PPV and NPV will be computed for the prostate gland and the lymph nodes in Cohort A subjects in the Evaluable Set. The normal approximation to the binomial distribution is planned assuming the assumptions have been met (See Section 7.2). PPV and NPV will be computed for each of the three central imaging core lab independent PET/CT readers.

7.7.2. PPV and Sensitivity in Cohort B

Point estimates and two-sided 95% CIs for PPV and Sensitivity will be computed from the conventional guided biopsy obtained from subjects in Cohort B for the Evaluable Set. The normal approximation to the binomial distribution is planned assuming a null hypothesis of 0.5. If the assumptions are not met, then confidence intervals derived from an Agresti-Coull exact test will be used (See Section 7.2). Results will be computed for each of the three central imaging core lab independent readers.

7.7.3. Detection Rates for Lesion Counts in both Cohorts Combined

For subjects in Cohort A and B combined, the sum of the lesions per tissue type and overall per subject will be summarized showing the N, mean, median, standard deviation, minimum and maximum values for each central imaging core lab reader including the reader of conventional scans. ^{18}F-DCFPyL images and conventional images will be summarized separately and the mean of each reader's results from ^{18}F-DCFPyL PET/CT will be compared to conventional imaging using a one-way repeated measures ANOVA. If the assumptions are not met for this test (see Section 7.2), then a Friedman's test will be performed to determine if there is a difference between any of the groups. If significant is determined from either the ANOVA or the Friedman's test, then a Dunnett's test will be performed to show where the difference exists between each reviewer and the conventional scan. A p-value and 95% confidence interval for the difference in means will be presented for each ^{18}F-DCFPyL PET/CT reviewer versus conventional imaging. This analysis will be performed on the Evaluable Set.

7.7.4. PK

Blood, plasma, and urine collection at each nominal time will be collected twice per patient. The mean of the values at each nominal time will be used in the creation of parameters used in the analysis. For each subject, blood concentration-time data using actual blood draw times rather than nominal times will be computed by non-compartmental analysis and pharmacokinetic parameters will be generated. Additional blood concentration-time data will be fitted into a two-compartment model to calculate $T_{1/2\text{-alpha}}$ and $T_{1/2\text{-beta}}$. Summary statistics for blood will be presented for maximum concentration (C_{max}), area under the (activity-time) curve (AUC), body weight normalized clearance (CL), volume of distribution at steady-state (V_{ss}), time to maximum concentration (T_{max}), half-life($T_{1/2}$) [noncompartmental analysis], T1/2-alpha and T1/2-beta [2-

compartment modelling], and mean residence time (MRT). Since there are two values collected per nominal time, the mean of these values within nominal time will be derived prior to generating the PK parameters. These PK parameters will be derived by an external analyst then summarized for the PK blood set. PSA groups, eGFR groups and eGFR will also be summarized for the PK blood set.

Summary statistics for urinary excretion will be presented for Tmax, Rate max, Rate last, T1/2elim, and Cumulative Urine Recovery. For % of injected dose recovered per each urine collection interval per subject will be used to calculate Tmax, Rate max, Rate last, $T_{1/2elim}$, and cumulative urine recovery by 4 and 8 hours post-administration if feasible. These PK parameters will be derived by an external analyst then summarized for the PK urine set. eGFR groups as defined in Section 5.5.16 and eGFR will also be summarized for the PK urine set.

The ratio of plasma-to-blood concentrations will be calculated per subject/time-point.

7.8. Analysis of Exploratory Endpoints

Sensitivity and specificity of the prostate gland as well as $SUV_{max,}$ SUV_{peak} and SUV_r will all be analyzed on the evaluable set. Change in Management defined from the questionnaire will be summarized on the safety set. The PPV endpoint will be analyzed on the Change in Planned Protocol Procedure Set.

- $SUV_{max,}$ SUV_{peak}, SUV_{mean}, and volume will be summarized for each tissue location (bone, lymph nodes, soft tissue, and prostate gland) and each of the 3 central imaging core lab independent readers using the evaluable set from both cohorts. SUV_r will be summarized in the same manner including a reference lesion also. A 95% confidence interval for the mean or distribution will be presented for each reader based on the assumption on normality defined in Section 7.2.
- Differences in the average across all 3 reviewers for $SUV_{max,}$ SUV_{peak}, $SUV_{r,}$ SUV_{mean}, and volume will be compared between histology outcomes using a t-test that assumes unequal variances. If the assumptions for the t-test are not met then a Wilcoxon rank sum test will be performed with corresponding exact 95% confidence intervals defined in section 7.2.
- The average $SUV_{max,}$ SUV_{peak}, $SUV_{r,}$ SUV_{mean}, and volume values across all reviewers will be compared between Gleason Score groups at time of radical prostatectomy, Baseline PSA groups and testosterone groups split at the median value. The comparisons of means between groups will be performed using a generalized linear model. If normality cannot be assumed then a Kruskal-Wallis test will be performed instead. Within each group a 95% confidence interval will be presented.
- Point estimates and two-sided 95% CIs for Specificity and Sensitivity will be computed from the prostate gland for Cohort A in the Evaluable Set. The normal approximation to the binomial distribution is planned assuming a null hypothesis of 0.5. If the assumptions are not met then confidence intervals derived from an Agresti-Coull exact test will be used (See Section 7.2). Results will be computed for each of the 3 central imaging core lab independent readers.

- Clinical management questions pre- and post ^{18}F-DCFPyL PET/CT imaging will be summarized from the questionnaire evaluated by a central reader. The proportion of subjects in Cohort A who had a change in intended clinical management plan from pre- to post PyL scans will be analyzed using a one sample binomial test.
- Point estimates and two-sided 95% CIs for PPV will be computed for the change of management set. An Agresti-Coull 95% confidence interval will be used will be used assuming a null hypothesis of 0.5. Results will be computed for each of the 3 central imaging core lab independent readers.

7.9. Reader Reliability

There are four imaging readers who were trained to perform our central reads used in much of the analyses. Only three of these readers will perform these reads with the fourth reader as an alternative if needed. Variability of these readers regarding the primary endpoint for the evaluable set will be tested as described below. The following is assumed:

N_i=total number of subjects with the primary endpoint in the evaluable set (i=1, 2,…N)
K=number of readers (3)
R_j= number of responses (j=1,2)
n_{ij}=number of times subject i is in response group j

7.9.1. Intra-Reader Reliability

Prior to reading any images, a random subset of 30 PyL images will be randomly selected by the Imaging vendor. Once the reads start, this subset will be re-introduced to each reader no sooner than 3 weeks after the original read. They will be read under identical conditions as the original read (same criteria evaluation, same analysis reporting, same analysis platform). The rate of agreement between the original reads and the re-reads for the primary endpoint in this subset will be compared using the intra-rater variability defined from Cohen's Kappa[5]. This calculation will be performed for each reader separately.

$$Cohen's\ Kappa = \frac{p_{a-}\, p_e}{(1-p_e)}$$

where $p_a = \sum_{j=1}^{R} \frac{n_{jj}}{n}$

$$p_e = \sum_{j=1}^{R} \frac{n_{j+}}{n}\frac{n_{+j}}{n}$$

The standard error of Kappa σ_k will be calculated as:

$$\sigma_k = \sqrt{\frac{P_a(1-P_a)}{N(1-P_e)^2}}$$

It is assumed that the concordance rate between time points for each reader will be at minimum of 93% with a Kappa of 86%. This would yield a 95% confidence interval of (0.68, 1) for a sample of 30 subjects.

7.9.2. Inter-Reader Reliability

For the primary analysis of the primary endpoint the inter-reader reliability will be estimated using the multiple-reader generalized kappa statistic developed by Fleiss[6,7].

$$Kappa = \frac{\bar{p} - \bar{p}_e}{1 - \bar{p}_e}$$

Variance: $\frac{2}{NK(K-1)} \frac{\sum_{j=1}^{R} p_j^2 + \left(\sum_{j=1}^{R} p_j^2\right)^2 - 2\sum_{j=1}^{R} p_j^3}{(1-\sum_{j=1}^{R} p_j^2)^2}$

Where

$p_j = \frac{1}{NK}\sum_{i=1}^{N} n_{ij}$

$p_i = \frac{\sum_{j=1}^{R} n_{ij}(n_{ij}-1)/2}{K(K-1)/2}$

$\bar{p} = \frac{\sum_{i-1}^{N} p_i}{N}$ (overall agreement)

$\bar{p}_e = \sum_{j=1}^{R} p_j^2$ (expected chance agreement)

The generalized Kappa statistic and a 95% confidence interval will be computed.

8. SAFETY AND TOLERABILITY

All safety data will be summarized by cohort.

8.1. Adverse Event Preferred Term and System Organ Class Summary Tables

An overall summary of frequency and percentage of treatment-emergent adverse events (TEAEs), most frequent (>5%) overall TEAEs, serious TEAEs, severe TEAEs (grade ≥ 3), TEAEs by grade, and treatment-related TEAEs will be presented by cohort and overall using the safety set.

8.1.1. Summaries of Adverse Event Incidence Rates for All Subjects

Treatment-emergent adverse events will be summarized by SOC and PT using the frequency and percentage of subjects experiencing any adverse event, experiencing each SOC and experiencing each PT within each SOC, using the safety set. The number of occurrences of each adverse event will be included.

Treatment-emergent adverse events will be summarized by severity and for subjects who report adverse events with severity grades 3 or higher. The most severe occurrence of each event will be summarized by SOC and PT using the frequency and percentage of subjects experiencing any adverse event, experiencing each SOC and experiencing each PT within each SOC by cohort and overall, using the safety analysis set.

Treatment-emergent adverse events will be summarized by relationship to study drug. The most closely related occurrence of each event will be summarized by SOC and PT using the frequency and percentage of subjects experiencing any adverse event, experiencing each SOC and experiencing each PT within each SOC by cohort and overall, using the safety analysis set.

8.1.2. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Discontinuations, and Death

The overall summary table includes incidences of serious adverse events, adverse events that led to discontinuation and deaths.

Separate listings for serious adverse events, adverse events that led to discontinuation and deaths will be created.

8.2. Exposure to Study Drug

Exposure to study drug will be summarized using summary statistics for volume administered, location of injection, correction factor at pre and post dose, the decay corrected dose in mCi and MBq at time of administration, and any dose change due to an AE for the safety set.

8.3. Concomitant and Other Medications

Concomitant medications will be summarized by ATC4 class and generic term using frequencies and percentages for the safety analysis set.

8.4. Routine Laboratory Data

Summary statistics for observed and change from baseline values of each laboratory analyte will be presented by visit for the safety set. Labs will include hematology and chemistry. A shift table will also be presented showing the shift in values from Baseline to follow up (below LLN, within LLN and ULN, above ULN, and missing). The following parameters will be created and summarized also:

Leukocytes = sum of Basophils, Eosinophils, Lymphocytes, Monocytes, and Neutrophils

Basophils/leukocytes = (Basophils/leukocytes)*100

Eosinophils/leukocytes = (Eosinophils /leukocytes)*100

Lymphocytes/leukocytes = (Lymphocytes /leukocytes)*100

Monocytes/leukocytes = (Monocytes /leukocytes)*100

Neutrophils/leukocytes = (Neutrophils /leukocytes)*100

8.5. Vital Signs

Summary statistics for observed and change from baseline values of each vital sign (systolic and diastolic blood pressures, heart rate, respiratory rate, and temperature) will be presented by visit and cohort for the safety set.

8.6. ECG

Summary statistics for observed and change from baseline values of each ECG parameter will be presented by visit and cohort using the safety set. For QT interval, adjudicated QTc-Bazett and adjudicated QTc-Fidericia, the following groups will be summarized at Baseline and the pre-imaging visit: values above 450, above 480 and above 500. For these same parameters the following will be summarized at the pre-imaging time point only: Increase 31-50, increase >60, decrease 31-60, and decrease >60.

8.7. Physical Examination

Not applicable

9. PHARMACOKINETICS

Summary statistics for blood will be presented for maximum concentration (Cmax), area under the (activity-time) curve (AUC), clearance (CL), volume of distribution at steady-state (Vss), time to maximum concentration (Tmax), half-life(T1/2) [noncompartmental analysis], T1/2-alpha and T1/2-beta [2-compartment modelling], and mean residence time (MRT). Clearance and Vss will be body-weight normalized.

Percent of dose recovered in urine will be presented by collection intervals for the PK urine set. The following urinary kinetics will also be presented for this set: Tmax, Rate max, Rate last, $T_{1/2\ elim}$, and cumulative urine recovery by 4 and 8 hours post administration as % injected dose. The ratio of plasma-to-blood concentrations will be calculated per each subject/time-point.

9.1. Derived Data

- Concentration of Reference Standard, μCi/mL =

  (Decay Corrected pre injection reference standard of syringe prior to injection into flask– Decay Corrected post injection reference standard of syringe after injection into flask)/1000mL.
- Reference Standard CPM = ^{18}F-DCFPyL reference standard (CPM) from PK*Decay Correction factor for measurement time defined for 0-4 hours
- Average CPM for Reference standard= Average of 3 CPM results collected for ^{18}F-DCFPyL std for 0-4 hours.
- Average CPM/ml for reference standard= Average CPM for reference standard/0.3
- Concentration of Reference Standard in CPM/μCi = Average CPM/ml for reference standard/concentration of reference standard (μCi/mL)
- For each blood, plasma and urine sample time, calculate:
  - ^{18}F-DCFPyL CPM_b = ^{18}F-DCFPyL CPM result at sample time*correction factor for measurement time defined for the PK period the sample is drawn in
  - CPM_b(ml) = CPM_b/0.3

  - CPM concentration(μCi/ml) = CPM_b (ml) / Concentration of Sample in CPM (μCi)
  - Average CPM μCi/ml = average CPM μCi/ml within each unique nominal time

- Ratio of plasma to blood = Average CPM (μCi/ml) for plasma/ Average CPM (μCi/ml) for blood per unique sample nominal time
- For each urine sample, calculate:
  - Radioactivity excreted per collection interval (μCi) = CPM (μCi/ml) from urine*urine collection volume (ml)
  - % Dose excreted = (Sum of Radioactivity exerted per collection interval(μCi) /(administered dose(mCi)*1000))*100
  - Average % dose excreted = average of individual % dose excreted per unique urine collection interval
  - Cumulative Average % dose excreted = sum of average % dose excreted over all unique urine collection intervals:
    - 0-4 hours = sum of average % dose excreted over 0-2 and 2-4 hours urine collection intervals
    - 0-8 hours = sum of average % dose excreted over all unique 0-2 and 2-4 hours urine collection intervals (0-2, 2-4, and 4-8 hours)
  -

Pharmacokinetic analyses will be conducted on pooled cohorts using the PK blood set and PK urine set.

10. PLANNED TREATMENT SAP CHANGES THAT DIFFER FROM THE PROTOCOL

- Screened population renamed to consented population as the definition states all subjects need to provide consent and not screening data.
- The Evaluable set was updated to state that subjects in Cohort A are required to have a prostatectomy and lymphadenectomy.
- The Change in Planned Protocol Procedure Set was added as a subject population to capture the subjects who had a change in the planned protocol procedure.
- The PK Evaluable set was divided into two groups: The PK Blood Set and the PK Urine set, as a subject could meet the criteria for one of these, but not the other.
- 'PPV of 18F-DCFPyL PET/CT imaging in subjects with corresponding histopathology that is outside the planned protocol surgical template or biopsy site' was updated to 'PPV of 18F-DCFPyL PET/CT imaging in subjects with corresponding histopathology for subjects who had a change in planned treatment per Cohort assignment'. Subjects may undergo a planned protocol procedure defined per the other cohort.
- The number of lesions per subject plotted against PSA and baseline testosterone for each of the 3 central imaging core lab readers will no longer be performed.
- $SUV_{max,}$ SUV_{peak}, SUV_r will no longer be summarized by subgroups: Previous radiation therapy (yes/no), Previous hormonal therapy (yes/no), or Previous chemotherapy (yes/no). Most subjects will be from cohort B only.
- Sensitivity will no longer be summarized by previous radiation therapy, previous hormonal therapy or previous chemotherapy. Since it is no longer the primary endpoint and it's not appropriate to combine cohorts for this analysis, it is no longer of interest.
- The following was added for PK: Additional blood concentration time data will be fitted into a two-compartmental model to calculate $T_{1/2\text{-alpha}}$ and $T_{1/2\text{-beta}}$. For % of injected dose recovered per each urine collection interval per subject will be used to calculate Tmax, Rate max, Rate last, $T_{1/2elim}$, and cumulative urine recovery if feasible.

11. REFERENCES

1. ICH E6: Good Clinical Practice: Consolidated Guidance
2. ICH E9: Statistical Principles for Clinical Trials
3. Fleiss, J. L.; Levin, B.; Paik, M.C. (2003). Statistical Methods for Rates and Proportions (3rd ed.). New York: John Wiley & Sons
4. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12
5. Gwet, K.; Intrarater Reliability. Wiley Encyclopedia of Clinical Trials, Copyright 2008 John Wiley & Sons, Inc.

6. Woolson, R.; Statistical Methods for the Analysis of Biomedical Data. Copywright 1987 John Wiley & Sons, Inc.
7. Fleiss, J. L., Nee, J. C. M., and Landis, J. R. Ž1979. The large sample variance of kappa in the case of different sets of raters. *Psychol*. *Bull*., 86, 974_977.

12. APPENDIX

12.1. Table of Contents for Data Display Specifications

Table 4 contains a list of tables, listings and figures proposed for this study.

Table 4: List of Tables, Listings and Figures

Number	Title
14.1-1	Subject Enrollment and Disposition, Consented Subjects
14.1.1: Baseline Summaries – Safety Set	
14.1.1-1	Demographics and Baseline Characteristics, Safety Set
14.1.1-2	Prostate Cancer History, Safety Set
14.1.1-3	Medical History, Safety Set
14.1.1-4	Prior Prostate Cancer Therapies, Safety Set
14.1.1-5	Prior Surgery, Safety Set
14.1.1-6	Conventional Imaging at Baseline, Safety Set
14.1.1-7	Baseline Medication Use, Safety Set
14.1.2: Baseline Summaries – Evaluable Set	
14.1.2-1	Demographics and Baseline Characteristics, Evaluable Set
14.1.2-2	Prostate Cancer History, Evaluable Set
14.1.2-3	Medical History, Evaluable Set
14.1.2-4	Prior Prostate Cancer Therapies, Evaluable Set
14.1.2-5	Prior Surgery, Evaluable Set
14.1.2-6	Conventional Imaging at Baseline, Evaluable Set
14.1.2-7	Baseline Medication Use, Evaluable Set
14.1.3: Baseline Summaries – Per Protocol Set	
14.1.3-1	Demographics and Baseline Characteristics, Per Protocol Set
14.1.3-2	Prostate Cancer History, Per Protocol Set
14.1.3-3	Medical History, Per Protocol Set
14.1.3-4	Prior Prostate Cancer Therapies, Per Protocol Set
14.1.3-5	Prior Surgery, Per Protocol Set
14.1.3-6	Conventional Imaging at Baseline, Per Protocol Set
14.1.3-7	Baseline Medication Use, Per Protocol Set
14.2.1: Primary Efficacy – Evaluable Set	
14.2.1-1	Sensitivity and Specificity of the Pelvic Lymph Nodes for the Subjects in Cohort A, Evaluable Set

14.2.2: Secondary Efficacy- Evaluable Set or PK Serum Set	
14.2.2-1	Diagnostic Testing for Secondary Endpoints, Evaluable Set
14.2.2-2	Summary of Imaging Detection Rates for Lesion Counts by Region- Evaluable Set
14.2.2-3	Summary of Pharmacokinetic Parameters for Cycle 1, Day1- PK Blood Set
14.2.3: Exploratory Efficacy	
14.2.3-1	SUV Responses at Baseline- Evaluable Set
14.2.3-2	SUVR Responses at Baseline – Evaluable Set
14.2.3-3	SUV Responses by Histology Outcomes- Evaluable Set
14.2.3-4	SUV Responses and Volume at Baseline by PSA Groups- Evaluable Set
14.2.3-5	SUV Responses and Volume at Baseline by Gleason Score Groups at Time of Prostatectomy- Evaluable Set
14.2.3-6	SUV Responses and Volume at Baseline by Testosterone Groups-Evaluable Group
14.2.3-7	Specificity and Sensitivity of the Prostate Gland for Cohort A- Evaluable Set
14.2.3-8	Shift in Change of Management Questionnaire- Safety Set
14.2.3-9	Analysis of Change in Management Questionnaire- Safety Set
14.2.3-10	PPV and Positive Imaging from any tissue compared to histology for both Cohorts Combined -Change in Management Set
14.2.3-11	Summary of Imaging Results-Safety Set
14.2.3-12	Summary of Histology Results- Safety Set
14.2.3-13	Summary of Procedures- Safety Set
14.2.3-14	Inter-Reader and Intra-Reader Variability for Cohort A- Evaluable Set
14.2.4: Efficacy- Per Protocol Set	
14.2.4-1	Specificity and Sensitivity of the Pelvic Lymph Nodes for the Subjects in Cohort A- Per-Protocol Set
14.3.1: Adverse Events- Safety Set	
14.3.1-1	Summary of Treatment Emergent Adverse Events, Overall and by Cohort -Safety Set
14.3.1-2	Most Frequent (>5% Overall) Treatment Emergent Adverse Events, Overall and by Cohort-Safety Set
14.3.1-3	Treatment Emergent Adverse Events Overall and by Cohort- Safety Set
14.3.1-4	Serious Treatment Emergent Adverse Events Overall and by Cohort- Safety Set
14.3.1-5	Drug Related Treatment Emergent Adverse Events Overall and by Cohort- Safety Set
14.3.1-6	Treatment Emergent Adverse Events where Severity Grade>=3, Overall and by Cohort-Safety Set
14.3.1-7	Treatment Emergent Adverse Events by Severity Grade, Overall – Safety Set

14.3.2: Listing of Deaths and Other Serious and Significant Adverse Events- Safety Set	
14.3.1-1	Listing of Treatment Emergent Adverse Event Leading to Discontinuation or Death- Safety Set
14.3.1-2	Listing of Treatment Emergent Adverse Events Deemed Serious or With a Grade 3 or Above- Safety Set
14.3.4: Abnormal Laboratory Value Listing	
14.3.4-1	Listing of Abnormal Hematology Results – Safety Set
14.3.4-2	Listing of Abnormal Chemistry Results- Safety Set
14.3.5: Vital Signs	
14.3.5-1	Summary and Change from Baseline in Vital Signs- Safety Set
14.3.6: Other Safety Data	
14.3.6-1	Summary and Change from Baseline in Hematology Results- Safety Set
14.3.6-2	Summary and Change from Baseline in Chemistry Results- Safety Set
14.3.6-3	Clinical Laboratory Shift Table: Chemistry- Safety Set
14.3.6-4	Clinical Laboratory Shift Table: Hematology- Safety Set
14.3.6-5	Summary and Change from Baseline in ECG Parameters- Safety Set
14.3.6-6	Concomitant Medications- Safety Set
14.3.6-7	Study Drug Exposure- Safety Set
14.4: PK Evaluations	
14.4-1	Percent of Dose Recovered in Urine per Collection Interval -PK Urine Set
14.4-2	Summary of Urinary Kinetics- PK Urine Set
Listings	
16.2.1-1	Listing of Discontinuations – Consented Population
16.2.2-1	Listing of Protocol Deviations – Safety Set
16.2.3-1	Listing of Subjects Excluded from the Evaluable Set Used for Efficacy- Safety Set
16.2.4-1	Listing of Demographics- Consented Set
16.2.5-1	Listing of Blood PK by Nominal Blood Draw Times – PK Blood Set
16.2.5-2	Listing of Plasma PK by Nominal Blood Draw Times- PK Blood Set
16.2.5-3	Listing of Blood PK Parameters- PK Blood Set
16.2.5-4	Listing of Urinary Kinetics- PK Urine Set
16.2.5-5	Listing of Urine PK by Collection Intervals- PK Urine Set
16.2.5-6	Listing of Decay Corrected Dose – Safety Set
16.2.5-7	Listing of Compliance- Safety Set
16.2.6-1	Listing of Diagnostic Performance – Evaluable Set

16.2.7-1	Listing of Adverse Events- Safety Population
16.2.8-1	Listing of Laboratory Parameters- Safety Set
Figures	
14.4.1	PK Concentrations by Nominal Time- PK Blood Set