STATISTICAL ANALYSIS PLAN
PHASE 3

NCT03739684

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DATE OF PLAN:

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STUDY DRUG:

^{18}F-DCFPYL (PyL)

PROTOCOL 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**)

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

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
ADT	Androgen Deprivation Therapy
AE	Adverse Event
BCR	Biochemical Recurrence
CI	Confidence Interval
CLR	Correct Localization Rate
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
GCP	Good Clinical Practices
ICH	International Council on Harmonisation
kg	Kilogram
LN	Lymph node(s)
MAR	Missing-at-random
MBq	megaBequerel
mCi	millicurie
MedDRA	Medical Dictionary for Regulatory Activities Terminology
mg	Milligram
MI	Multiple imputation
mL	Milliliter
MMQ	Medical Management Questionnaire
MRI	Magnetic Resonance Imaging
N	Total Sample Size
ng	Nanogram
PET	Positron Emission Tomography
PP	Per-Protocol Population
PPV	Positive Predictive Value
PSA	Prostate-specific Antigen
PT	Preferred term
PyL	^{18}F-DCFPyL

RP	Radical prostatectomy
RT	Radiation therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUV	Standardized uptake value
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol PyL-3301. This SAP was developed in accordance with ICH E9 guideline[1]. All decisions regarding final analysis, as defined in this SAP document, will be made prior to database lock unless communicated to the governing Regulatory Authority. Further information can be found in the protocol.

3. STUDY OBJECTIVES

3.1. 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

3.2. 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

3.3. 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

4. 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 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 ^{18}F-DCFPyL PET/CT scans per local interpretation (detection of disease at any location) will be followed for Efficacy follow-up visit(s) (See Table 1 Schedule of Assessments). ^{18}F-DCFPyL PET/CT scans will be evaluated by three independent central readers blinded to all clinical and other imaging information. ^{18}F-DCFPyL PET/CT imaging results reported by the central readers will be compared to the composite truth standard of histopathology where available, imaging follow-up, or treatment response as defined in Section 5.1.1.

Once the study reaches the required number of subjects evaluable for calculation of the primary endpoint as described in Section 7.1, 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 planned 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 a planned change to the initial medical management plan is warranted due to the PyL finding.

The study Schema is in Figure 1 and the Schedule of Assessments is in Table 2

Figure 1: Study Schema

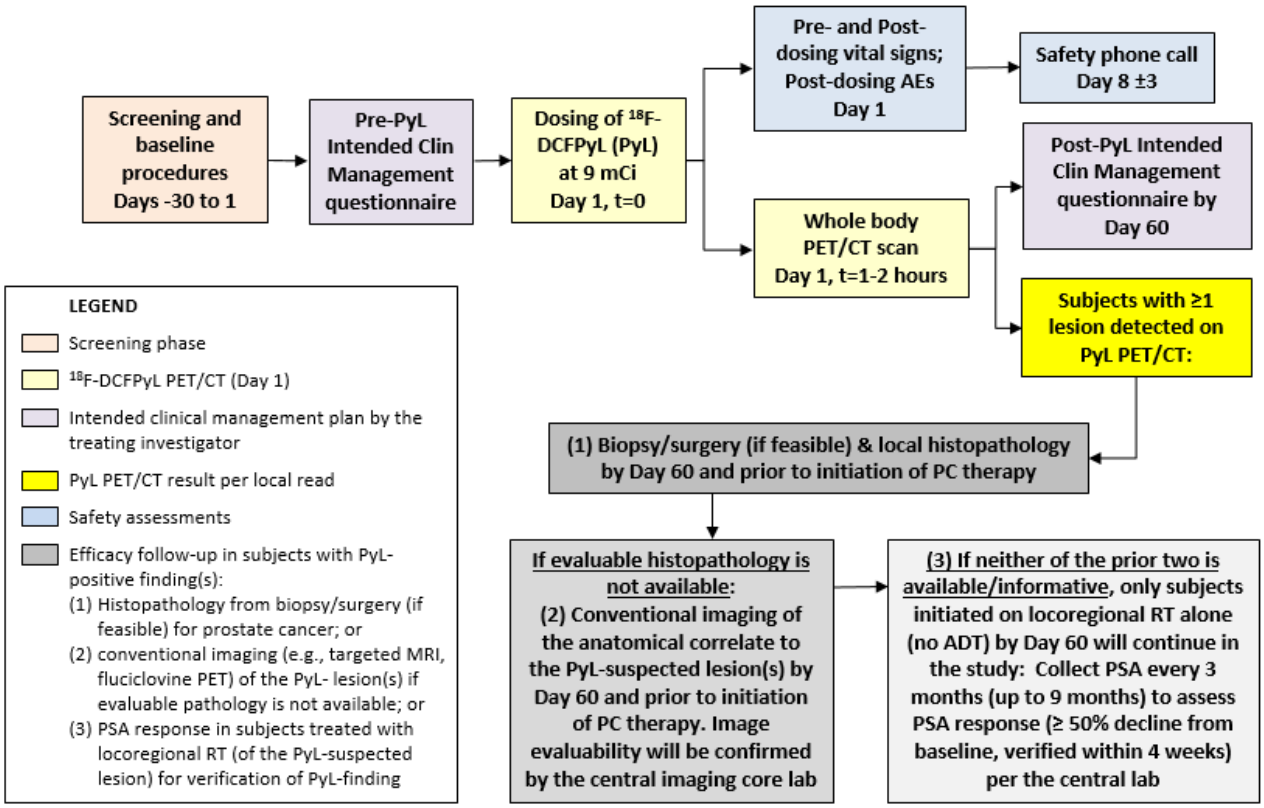

Table 2: Schedule of Assessments

	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

	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]**
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. STUDY ENDPOINTS

5.1. Efficacy Endpoints

Efficacy endpoints that reference ^{18}F-DCFPyL PET/CT imaging findings are based on imaging results as reported by central imaging review by three independent, blinded central readers. The primary endpoint of CLR and the exploratory PPV endpoints are also based on the assessments made by the Imaging Truth Panel (a consensus of two readers distinct from the independent central PyL readers). See the study Imaging Review Charter for read paradigm and details. The change in clinical management endpoint is based on investigator assessment of local ^{18}F-DCFPyL PET/CT imaging findings.

5.1.1. Primary Endpoint

The primary endpoint of the CLR is evaluated in a subset of Full Analysis Set (FAS) subjects with at least one positive lesion identified by ^{18}F-DCPyL PET/CT imaging by the local reader and then evaluated against the composite truth standard by three independent, blinded central imaging readers. 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 (by central review) and the composite truth standard, which is 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., ^{18}F-fluciclovine PET (preferred if was not performed at baseline) or choline PET; 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 is 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.

The CLR in percent 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 evaluated by at least one central reader and a positive result on the composite truth standard in the following order of importance:

- Positive finding for prostate cancer of a PyL-suspected lesion according to local histopathology (confirmed by at least one anatomical correlate will suffice to declare the PyL PET/CT assessed by the central reader defining a true positive), or
- Positive finding for prostate cancer of a PyL-suspected lesion upon follow-up correlative imaging by CT, MRI, whole body bone scan, NaF, fluciclovine or choline PET/CT

performed following PyL PET/CT (one confirmed anatomical correlate will suffice to declare the PyL PET/CT assessed by the central reader a true positive), or

- PSA decreases by ≥50% from baseline following RT (without concomitant ADT) up to nine months following initiation of such treatment if the other two truth standards were not performed or did not provide evaluable results

False positives will be defined as subjects with positive lesion(s) on PyL PET/CT from at least one central reader who has 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 correlative imaging performed following PyL PET/CT, or
- PSA does not decrease by ≥50% from baseline following RT (without concomitant ADT) up to 9 months following initiation of such treatment.

The CLR lesion location(s) will be matched with the CLR lesion location(s) identified by the composite truth standard to determine if colocalization is successful, denoting a true positive (TP) assessment. If a subject has more than one lesion identified by pathology or by correlative imaging, then at least one lesion must be successfully colocalized for the subject to be considered a TP. The anatomic regions and CLR lesion locations matched by laterality (right or left) where applicable are presented in Table 3. The pelvic lymph nodes are grouped together for analysis in alignment with the data collected in the PyL-2301 (OSPREY) study. Within the prostatic region and extra-pelvic lymph nodes, specific CLR lesion location groupings are further modified specific for PET/CT findings based on Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE)[2] intended to guide reproducibility, general applicability and clinical relevance.

Table 3: Lesion Locations and Anatomic Regions

Anatomic Region	CLR Lesion Locations
Prostatic	Prostate gland or prostate bed (including seminal vesicles)
Pelvic Lymph Nodes	• Right Pelvic (including Internal Iliac [Hypogastric], External Iliac, Common Iliac, Obturator) • Left Pelvic (including Internal Iliac [Hypogastric], External Iliac, Common Iliac, Obturator) • Other pelvic (including Rectal/perirectal and Presacral)
Extra-pelvic (Lymph Nodes)	• Retroperitoneal (including Para/Peri-Aortic R/L and Celiac axis R/L) • Supradiaphragmatic (including Supraclavicular R/L, Pre/Paratracheal R/L, Posterior Mediastinal R/L, Anterior Mediastinal R/L, Subcarinal, Paracardiac R/L, Retrocrural R/L, Thoracic Hilar R/L, Mesenteric R/L, Axillary R/L, Cervical R/L)

Anatomic Region	CLR Lesion Locations
	• Other extra-pelvic (specify, including Inguinal/Femoral R/L)
Extra-pelvic (Bone)	• Pelvic bone R/L • Skull • Clavicle R/L • Scapula R/L • Sternum • Ribcage R/L • Spine (including cervical/thoracic/lumbar/sacral) • Extremities (including right upper, right lower, left upper, left lower) • Other bone lesion
Extra-pelvic (Visceral/soft-tissue)	• Lung/pleura • Liver • Other visceral/soft tissue lesion (including spleen, adrenal, mediastinum, pericardium, non-nodal retroperitoneal tissue, and other visceral/soft-tissue)

Each subject will be evaluated for the primary endpoint using a single truth standard source. If a subject has more than one source, e.g., undergoes correlative imaging and needle-guided biopsy, the pathology result from the needle biopsy will be evaluated as the truth standard. If the pathology result is unevaluable or the biopsy needle is not in a positive PyL lesion, then the results of the correlative imaging will be used as the truth standard.

Subjects with positive ^{18}F-DCFPyL PET/CT scans per local scan interpretation (detection of disease at any location) will be followed at the Efficacy visit(s) based on their ^{18}F-DCFPyL PET/CT finding(s) (see Section 4). If a subject has a negative ^{18}F-DCFPyL scan by the local interpretation, then no standard of truth data will be submitted by the study site and no efficacy evaluation will be performed by the central Truth Panel readers. If the subject's ^{18}F-DCFPyL PET/CT scan is interpreted as positive by one or more of the central readers and no standard of truth data is available for evaluation, then the subject will be considered unevaluable for the primary endpoint. Please see Section 5.1.3 for subjects with positive ^{18}F-DCFPyL scans by local interpretation where the central reader(s) identify the scan as negative.

Subjects with positive ^{18}F-DCFPyL PET/CT scans (by central review) will be classified as TP, FP or unevaluable as presented in Table 4.

Table 4: Primary Endpoint Assessment

Composite Truth Standard Source	Truth Standard Location Result	Central PyL Reader Location Match	Subject Outcome
Surgical pathology	Positive	Yes	TP
Surgical pathology	Positive	No	FP
Surgical pathology	Negative	Yes or No	FP

Composite Truth Standard Source	**Truth Standard Location Result**	**Central PyL Reader Location Match**	**Subject Outcome**
Surgical pathology	Unevaluable	Yes or No	Unevaluable, evaluate with another truth standard
Image guided biopsy, needle or tissue sampling device in PyL positive lesion	Positive pathology in the same anatomic region as at least one PyL positive lesion	Yes	TP
Image guided biopsy, needle or tissue sampling device in PyL positive lesion	Negative pathology in the same anatomic region as at least one PyL positive lesion	Yes	FP
Image guided biopsy, needle or tissue sampling device **not** in PyL positive lesion	Positive or negative pathology in the same anatomic region as at least one PyL positive lesion	Yes or No	Unevaluable, evaluate with another truth standard
Image guided biopsy, sampling method confirmation is not applicable or the confirmatory image is unevaluable	Positive or negative pathology in the same anatomic region as at least one PyL positive lesion	N/A	Unevaluable, evaluate with another truth standard
Correlative imaging (Truth Panel assessment)	Correlative Imaging result positive	Yes	TP
Correlative imaging (Truth Panel assessment)	Correlative Imaging result positive	No	FP
Correlative imaging (Truth Panel assessment)	Correlative Imaging result negative	Yes	FP
Correlative imaging (Truth Panel assessment)	Correlative Imaging unevaluable	Yes or No	Unevaluable, evaluate with another truth standard
PSA response following locoregional RT	Observed ≥ 50% decrease from baseline up to 9 months from start of RT, but response not confirmed	N/A	Unevaluable
PSA response following locoregional RT	Radiation therapy not directed to all PyL suspected lesions	N/A	Unevaluable

Composite Truth Standard Source	Truth Standard Location Result	Central PyL Reader Location Match	Subject Outcome
PSA response following locoregional RT	Confirmed ≥ 50% decrease from baseline at or before 9 months from start of RT	N/A	TP
PSA response following locoregional RT	No observed ≥ 50% decrease from baseline up to 9 months from start of RT, but PSA results are available	N/A	FP

N/A: not applicable

Lesion mismatches are defined as False Positives due to the subject having a positive finding (by Central PyL read) on the PyL scan.

5.1.2. Secondary 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 (based on local reader interpretation) (see Section 8.5.3).

The endpoint is the percentage of subjects with a change in intended prostate cancer treatment plan from Pre- and Post ^{18}F-DCFPyL PET/CT scan assessed using the MMQ, based on local ^{18}F-DCFPyL PET/CT scan read results, as the decision to change the subject's treatment plan or not to change plans is made using this data.

Any change in planned management, whether from no treatment to any treatment, from one treatment to another between treatment categories or within a treatment category will be tabulated as a change. Change vs. no change will be analyzed as a binary response.

The shifts between no planned treatment and the major categories of planned therapy as well as between those categories are defined in Table 5.

Table 5: Changes in Planned Therapy

Pre-^{18}F-DCFPyL PET/CT scan	Post-^{18}F-DCFPyL PET/CT scan
No treatment planned	Any treatment planned
Any treatment planned	No treatment planned
Treatment planned - local therapy	Treatment planned - systemic therapy
Treatment planned - systemic therapy	Treatment planned - local therapy
Treatment planned - local therapy	Treatment planned - other therapy
Treatment planned – systemic therapy	Treatment planned - other therapy
Treatment planned – other therapy	Treatment planned – systemic therapy
Treatment planned – other therapy	Treatment planned – local therapy

5.1.3. Tertiary/Exploratory Endpoints

- **Detection Rates by Anatomic Region**

The detection rate is defined as the percent of positive ^{18}F-DCFPyL PET/CT scans identified by the central imaging readers. It is calculated as the number of subjects with positive scans divided by the number of subjects who have evaluable scan results reported times 100. For this analysis, if a subject has a PyL positive scan in any of the anatomic regions defined in Table 3: prostatic, pelvic, extra-pelvic lymph nodes, extra-pelvic bone and extra-pelvic other, then the subject will be counted within the respective region. Another tabulation will assess detection rates in the prostatic, pelvic and extra-pelvic regions, where all extra-pelvic regions (lymph node, bone and other tissue) will be combined. If a subject has lesions detected in more than one anatomic region, then that subject will be counted for all respective regions.

- **PPV by Anatomic Region**

The PPV for subjects with positive ^{18}F-DCFPyL PET/CT scans is defined as the percent of subjects with true positive results divided by all subjects with ^{18}F-DCFPyL PET/CT scans or TP/(TP+FP)00%. For this analysis, the subject will be designated as a TP if the ^{18}F-DCFPyL PET/CT scan identified by the central imaging readers has at least one lesion and the respective truth standard result has a positive finding in the respective regions as defined in Table 3: prostatic, pelvic, extra-pelvic lymph nodes, extra-pelvic bone and extra-pelvic other. Another tabulation will assess PPV in the prostatic, pelvic and extra-pelvic regions, where all extra-pelvic regions (lymph node, bone and other tissue) will be combined. If a subject has lesions detected in more than one anatomic region, then that subject's results will be included in all respective regions.

- **False Positive Scan Rates**

Subjects with false positive scans are defined as subjects with positive ^{18}F-DCFPyL PET/CT scans identified by a central reader who do not have confirmation of any lesions by a truth standard. The false positive rate is calculated as the number of subjects with positive scans defined by the central imaging reader without confirmation by any truth standard, divided by the number of subjects who have positive scan results times 100.

- **Detection Rates by Baseline PSA**

In addition to presenting detection rates by anatomic region of the lesions, detection rates of any PyL positive lesion at the subject level identified by the central imaging readers will be summarized for all subjects grouped by baseline PSA values categorized as: < 0.2 ng/mL, 0.2 to < 0.5 ng/mL, 0.5 to < 1 ng/mL, 1 to <2 ng/mL, 2 to <5 ng/mL and ≥5 ng/mL.

- **False Negative and True Negative Subjects**

Subjects may have a positive PyL scan by local interpretation and available truth standard data, but the central readers identify the scan as negative. If this situation arises, the following rules will apply:

- If the central reader classifies the scan as negative and the truth standard is positive, then the subject will be considered a false negative

- If the central reader classifies the scan as negative and the truth standard is negative, then the subject will be considered a true negative

- **True Positive Detection Rate**

The overall true positive detection rate (TPR) is the rate of subjects with positive ^{18}F-DCFPyL PET/CT scans identified by a central reader confirmed to have a positive SOT (ie, a true positive [TP] subject) divided by the total number of subjects who had a ^{18}F-DCFPyL PET/CT scan interpreted by a central reader times 100. This represents the total fraction of true positive subjects, or TP/ (TP+FP+TN+FN), where the sum of negative PyL scans (TN+FN) are reported even if the specific breakdown of TN and FN numbers may be unknown.

5.2. 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
- Summary of concomitant medications and procedures

5.3. Pharmacokinetic Endpoints

There are no pharmacokinetic data or endpoints in this study.

6. ANALYSIS POPULATIONS

6.1. Consented Population

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

6.2. Safety Population

The safety population includes all subjects who receive any amount of ^{18}F-DCFPyL.

6.3. Full Analysis Set (FAS) Population

The full analysis set consists of subjects who have received any amount of ^{18}F-DCFPyL and have ^{18}F-DCFPyL PET/CT imaging results from at least one central reader.

6.4. Per-Protocol (PP) Population

The per protocol population consists of the FAS excluding subjects with major protocol violations. Major protocol violations will be defined prior to performing the analysis of the study following database lock. The reasons for excluding subjects from the per protocol population (PP) will be included in a subject data listing of all protocol deviations.

7. SAMPLE SIZE

7.1. Sample Size Justification and Calculation

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 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 5.1.1

The assumed CLR of ^{18}F-DCFPyL PET/CT imaging is 30%. Based on the varied published experience with ^{68}Ga-PSMA PET/CT and a meta-analysis by Perera *et al*[3], 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 literature for ^{68}Ga-PSMA PET and the present study entry criteria, approximately 30% of PSMA PET/CT positive findings may be verified by biopsy/surgery-based histopathology, conventional imaging, or PSA follow-up post-RT.[4-7] 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 underlying target 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,[8,9] [4] 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.

7.2. Interim Analyses

There are no interim analyses planned for this study.

8. STATISTICAL ANALYSIS AND DATA CONVENTIONS

8.1. Computer Software

All analyses will be performed using SAS® Software, version 9.4 or later. nQuery Advanced and Microsoft Excel were used in performing the sample size calculations. Additional software may be used if appropriate. If used, all additional software products will be noted in the Clinical Study Report.

8.2. Data Presentation Conventions

Continuous variables will be presented using descriptive statistics (the number of subjects with available data, the mean, standard deviation (SD), median, minimum and maximum values). Categorical data will be summarized by the counts and respective percentages.

8.3. Baseline Characteristics

8.3.1. Baseline Definition

The subjects are required to have a pre-treatment PSA sample submitted to the central laboratory. If more than one sample is included in the CRF, the baseline value is the last value obtained prior to study drug administration. The baseline vital signs values will be the last measurements obtained prior to dosing.

Each subject is required to have baseline standard-of-care conventional imaging performed within 60 days of study drug administration. All imaging studies performed prior to administration of ^{18}F-DCFPyL will be considered as baseline.

8.3.2. Subject Disposition

A disposition table will be presented to show the number and percentage of subjects in each analysis population. All early discontinuations will be presented with the respective reasons. All subjects who sign informed consent will be accounted in the disposition summary.

8.3.3. Demographic and Baseline Characteristics

The subjects will undergo a prostate treatment assessment prior to dosing, using the Medical Management Questionnaire. The responses to each question on the questionnaire will be summarized for all subjects in the safety population.

8.3.4. Medical History

All relevant medical history other than the subject's prostate cancer history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.1). Medical history will be summarized by the number and percent of subjects in the safety population by system organ class (SOC) and unique Preferred Term (PT).

8.3.5. Prior Prostate Cancer Treatments

The subjects' prior treatments for prostate cancer will be summarized including surgical procedures, prior radiation therapies and systemic therapies (medications). Prior medications will

be coded using the World Health Organization drug dictionary (WHO-DDE Sep 2018). Prior surgical procedures are categorized as radical prostatectomy (RP), RP with pelvic lymph node dissection, pelvic lymph node dissection alone, Trans-urethral resection of prostate (TURP), and other procedures. radiation therapy is categorized as external beam radiation, brachytherapy and other therapies. The sites of radiation are prostate/prostate bed, pelvic non-prostatic lesions, and extra-pelvic lesions. Summaries will be prepared and will present the number and percent of subjects in the safety population who have these respective therapies recorded on their case report forms. Prior medications will be presented by ATC4 class and preferred term. Prior surgical and radiation therapies will be summarized by MedDRA SOC and preferred term. The time from original prostate cancer diagnosis to study entry (date of informed consent) in months will be summarized, as will the time from each reported prior therapy to study start. A month is defined as (difference in dates /365.25*12.). If partial dates(s) if diagnosis or treatments are reported, then a missing day will be set to the 15th of the month and a missing month will be set to July.

8.4. Missing Efficacy Endpoints

Missing values will not be replaced for any endpoint. There should be no missing primary endpoint values for subjects with evaluable PyL scans as assessed by the central readers unless no follow-up standard of truth (SOT) was completed. The subjects will be classified as true positive, false positive, or unevaluable. If a subject undergoes PyL imaging and does not have any follow-up evaluations or if the follow-up assessments are deemed unevaluable by the central readers based on image quality or other reasons, then that subject will be considered as unevaluable.

Exploratory evaluations of the primary endpoint will be performed using multiple imputation methods to examine the impact of missing or unevaluable SOTs for subjects with positive PyL scans as interpreted by the central readers. These methods are described in detail in section 8.5.2.2.

8.5. Efficacy Analysis

8.5.1. General Considerations

8.5.1.1. Testing Statistical Assumptions

The assumption underlying the normal approximation to the binomial distribution, used in the computation of the confidence intervals for CLR, PPV and detection rates 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 within a group. It is expected that the sample size for each statistic will be sufficient to meet this assumption. If the sample size is not sufficient, Agresti-Coull exact methods will be used.

8.5.2. Analysis of the Primary Efficacy Endpoint

The FAS will be used to analyze the primary analysis of the primary endpoint. The per protocol set will also be performed as a supplemental analysis of the primary endpoint.

8.5.2.1. Primary Analysis of Primary Endpoint

The primary endpoint is the CLR at the subject level, defined as the percentage of subjects with positive ^{18}F-DCFPyL PET/CT imaging from the central reads for whom there is a one-to-one correspondence between the CLR lesion location of at least one lesion identified on ^{18}F-DCFPyL PET/CT imaging and the composite truth standard, computed as 100×TP/(TP+FP). There are three independent central ^{18}F-DCFPyL PET/CT readers who will report whether each subject's PET/CT scan is positive or negative and will indicate the location(s) of the lesion(s) for all positive scans. The location(s) of the lesions will be matched with the standard of truth to determine if colocalization is successful, denoting a true positive (TP) assessment. If a subject has more than one lesion identified by pathology or by correlative imaging, then at least one lesion must be successfully colocalized for the subject to be considered a TP. The lesion locations for analysis as well as anatomic regions are defined in Table 3 in section 5.1.1.

PyL images obtained for subjects will be evaluated by three central readers. The results for all subjects will be summarized for each reader. The CLR is computed as TP/(TP+FP) *100% for each reader across all evaluable subjects. The respective two-sided 95% confidence interval for each reader will be computed using the binomial approximation to the normal distribution for each central reader. If the lower bound of the 95% CI is >0.2 for at least two of the three independent imaging reviewers, then the primary endpoint analysis is considered a success.

8.5.2.2. Sensitivity Analyses of the Primary Endpoint

The primary endpoint analysis will be repeated for subjects in the per-protocol analysis set, which excludes subjects with major protocol deviations.

There will also be an analysis of the primary endpoint for subjects who have positive ^{18}F-DCFPyL scans as reported by local interpretation. These subjects will have their endpoint evaluated following the same criteria as described in Table 3. The CLR and its corresponding 95% confidence interval will be calculated in the same manner as for the three independent central PyL readers. If there are more subjects with positive PyL scans identified by the central readers than those identified by the local readers, then a population of subjects with positive scans by local read results may be used.

There will be an analysis of the primary endpoint in the full analysis set with positive ^{18}F-DCFPyL PET/CT imaging as assessed by the central imaging readers, where the CLR lesion location recorded for pelvic lymph nodes will be grouped according to the PROMISE - standardized lymph node template[2] (internal iliac left, internal iliac right, external iliac left, internal iliac right, obturator left, obturator right, common iliac left, common iliac right, presacral and other pelvic lymph nodes). All other CLR lesion locations will be assessed, including laterality where applicable, as described in Table 3.

There will be an analysis of the primary endpoint in the full analysis set with positive ^{18}F-DCFPyL PET/CT imaging as assessed by the central imaging readers, where the specific lesion location recorded on the case report form, including laterality where applicable, is used instead of the CLR lesion location as described in Table 3.

A summary table will present the number and percent of subjects with either false negative or true negative outcomes for each central imaging reader. A data listing of subjects in these endpoint categories will also be prepared.

As noted in section 8.4, pattern mixture model-based multiple imputations (MI) assuming data are missing-at-random (MAR) and tipping point analyses will be performed as sensitivity analyses to examine the influence of the missing or unevaluable SOTs for subjects who have ^{18}F-DCFPyL PET/CT results reported by a central reader.[10] The locations of lesions as identified by the central reader(s) will be imputed as the lesion locations in the multiple imputation scenarios.

- Subjects with positive ^{18}F-DCFPyL PET/CT findings and missing or unevaluable standards of truth (SOTs) will have SOT responses imputed. Imputations of SOT responses will employ a pattern mixture model based multiple imputation method, assuming the data are MAR. The subjects with unevaluable SOTs will have responses imputed along with those subjects with SOT data within similar baseline PSA groupings (< 0.2 ng/mL, 0.2-<0.5 ng/mL, 0.5-< 1 mg/mL, 1-<2 ng/mL, 2-<5 ng/mL and ≥5 ng/mL). SAS PROC MI will be used, and 100 imputations will be performed for each of the three central readers.
- A second sensitivity analysis will impute SOT responses for subjects with positive ^{18}F-DCFPyL scans with missing/unevaluable SOT data by sampling from subjects with SOT results by method of SOT, including histopathology, Axumin scan, CT and MRI. If a subject has an unevaluable SOT result, then results from subjects with that same SOT will be used as the basis of the imputation pool. For subjects with no SOT, they will have results imputed with results of subjects with biopsy or surgery with histopathology, Axumin, CT and MRI scans separately.
- A tipping point analysis[11] will be performed to examine the multiple imputation method described by baseline PSA grouping. A group of delta (δ) values $(-0.95, -0.90, \ldots, -0.10, -0.05)$ will be used. After the imputed datasets are obtained from the multiple imputation for each central reader's result, the predicted responses will be estimated within each imputed dataset; applying the delta adjustment to the predicted probability of response for those subjects who had missing or unevaluable SOT results by adding δ, then generating random variates following a Bernoulli distribution. This will create a delta adjusted predicted probability within each imputed dataset. For a given delta, the above imputations should produce 100 CLR estimates for each central reader.

The results for all imputation analyses noted above will be combined using SAS PROC MIANALYZE and estimates of CLR and their respective 95% confidence intervals will be reported for each central reader.

8.5.2.3. Subgroup Analyses

The primary endpoint analysis will be performed for the following subgroups:

- Truth standard category: histopathology, correlative imaging, PSA response following locoregional RT
- Truth standard of each correlative imaging method
- Age: <65, ≥65
- Race: White, Black or African American, Other
- Ethnicity: Not Hispanic or Latino, Hispanic or Latino

- Baseline PSA, categorized as < 0.2 ng/mL, 0.2-<0.5 ng/mL, 0.5-<1 ng/mL, 1-<2 ng/mL, 2-<5 ng/mL, ≥5 ng/mL and the same PSA categories by historical therapy modality (prostatectomy alone, prior radiation therapy, both prostatectomy and prior radiation therapy)
- Historical initial therapy modality(ies) for prostate cancer at study entry: surgery (radical prostatectomy), radiation therapy (to the prostate gland), surgery and radiation therapy, prior androgen deprivation therapy (ADT), ADT and radiation therapy
- Baseline Screening imaging modality, categorized as fluciclovine PET/CT, choline PET, NaF PET, Pelvic CT/MRI, Abdomen CT/MRI, Chest CT/MRI, bone scintigraphy
- Study center: the distribution of treated subjects by center will be created at the end of the study. Small centers with five or fewer treated subjects may be combined into one or more centers for analysis.
- Size of largest lesion (long axis) detected on the PyL image by the central imaging readers: 0-<0.5 cm, 0.5-<1.0 cm, ≥1.0 cm
- Maximum standard uptake value (SUVmax) reported for the subject's lesion(s) on the PyL image by the central imaging readers: ≤2, 2-<5, 5-<10, ≥10
- Time of PyL scan following dosing: < 60 minutes, 60-<90 minutes, 90-≤ 120 minutes, > 120 minutes
- Time since discontinuation of ADT until study entry for subjects with prior ADT use

Subgroup analyses will be performed by tabulating the primary endpoint for each subgroup. For the analysis of the endpoint by SUVmax the tabulations will use the SUVmax value adjusted for lesion long axis. This value is the predicted SUVmax from a logistic regression model of CLR (0=No,, 1=Yes) for subjects with a positive PyL scan as assessed by the central reader, including SUVmax and lesion size (long axis as reported by the central reader). This analysis will be used if the lesion size term is significant at an alpha of 0.05. If the lesion size term is not significant the unadjusted SUVmax values will be used as reported by the central reader in the tabulations.

8.5.2.4. Multiple Comparisons and Multiplicity

There will be no correction for multiple comparisons as there is a single primary endpoint based on a composite truth standard where each subject is evaluated with only a single truth standard source.

8.5.3. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoint, change in planned medical management, will be generated on the FAS for all subjects regardless of finding(s) on PyL PET/CT imaging, and be analyzed by calculating a two-sided 95% CI for the proportion of subjects with any change in planned management as a binary variable. The summary will present the respective proportions and CIs calculated using a normal approximation to the binomial distribution if the statistical assumptions are met.

The analysis will present the percentage of subjects with a shift between no planned treatment and the major categories of planned therapy as well as between major categories defined in Table

5 by the local imaging readers' results and for all subjects combined. An additional tabulation will be presented for the changes in planned therapy between major categories of therapy by the results reported by the central PyL readers

A summary of shifts in planned management from Pre- and to Post- ^{18}F-DCFPyL imaging evaluations will also be presented for shifts between the specific categories of treatments within local therapies (Table 6). These shifts will also be summarized by the results of the local reader of the PyL scan and by the results reported by the three central readers.

Table 6: Shifts in Planned Therapy

Pre-^{18}F-DCFPyL PET/CT scan	**Post-^{18}F-DCFPyL PET/CT scan**
No treatment planned	Focal therapy
Focal therapy	No treatment planned
No treatment planned	Salvage surgery
Salvage surgery	No treatment planned

Another presentation of the change in planned management of the subject's disease will be a tabulation of all post-dose treatments against the pre-dose assessment.

The shifts within individual categories as well as an all shifts from pre- to post-PyL scan assessments will be presented with the number and percent of subjects with the respective change in shift tables, by the results reported by the local and central PyL readers. All pre- and post-PyL scan assessments will be presented with the assessment of change in a data listing.

8.5.4. Analysis of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints will be generated using the FAS to calculate 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. If a subject has more than one truth standard modality, (i.e., an image-guided biopsy and a correlative imaging scan) the information from the modality(ies) not used for the primary endpoint will be utilized in the calculation of exploratory endpoints. As there are results reported for three independent readers, these summary tables will present the respective endpoints for each reader.

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

- Detection rates of ^{18}F-DCFPyL PET/CT imaging by lesions in the following regions: prostatic, pelvic, extra-pelvic lymph nodes, extra-pelvic bone and extra-pelvic other defined in Table 3 in Section 8.5.2.1
- Detection rates of ^{18}F-DCFPyL PET/CT imaging by lesions in the following regions: prostatic, pelvic, extra-pelvic (lymph nodes, bone and other combined) defined in Table 3 in Section 8.5.2.1
- The detection rates of ^{18}F-DCFPyL PET/CT imaging as a function of baseline PSA groups categorized as <0.2 ng/mL, 0.2-< 0.5 ng/mL, 0.5-<1 ng/mL, 1-<2 ng/mL, 2-<5 ng/mL, ≥5 ng/mL

- Detection rates of ^{18}F-DCFPyL PET/CT imaging by baseline Screening imaging modality, categorized as fluciclovine PET/CT, choline PET, NaF PET, Pelvic CT or MRI, Abdomen CT or MRI, Chest CT or MRI, bone scintigraphy
- The percentage of subjects with positive ^{18}F-DCFPyL PET/CT scans assessed by the central reader who have negative findings for prostate cancer (false positive subjects) based on the composite truth standard. The percentage of false positive scans is defined as (1-CLR).
- The PPV of ^{18}F-DCFPyL PET/CT for prostatic, pelvic, extra-pelvic lymph nodes, extra-pelvic bone and extra-pelvic other regions defined in Table 3 in Section 8.5.2.1, based on the composite truth standard in subjects with positive lesion(s) on ^{18}F-DCFPyL PET/CT imaging
- The PPV of ^{18}F-DCFPyL PET/CT for prostatic, pelvic and extra-pelvic (lymph nodes, bone and other combined) regions defined in Table 3 in Section 8.5.2.1, based on the composite truth standard in subjects with positive lesion(s) on ^{18}F-DCFPyL PET/CT imaging
- The overall true positive detection rate (TPR) based on all subjects with a positive ^{18}F-DCFPyL PET/CT regardless of positive or negative findings as assessed by the central reader, as defined in section 5.1.3. This result will be reported on the primary endpoint table.

8.5.5. Other Efficacy Data

Summaries will be created for the following recorded measurements:

- Pathology results by lesion location and region
- Imaging results by lesion location and anatomic region for the central imaging readers, the imaging truth panel and the local site interpretation
- Lesion sizes by lesion location as recorded by the central imaging readers (and Imaging Truth Panel), excluding lesions indicated as unmeasurable
- SUV_{max}, and SUV_{mean} as recorded by the central imaging readers by lesion location
- The number of lesions detected per subject per CLR lesion location and per region (prostatic, pelvic, extra-pelvic)

8.5.6. Intra- and Inter-reader Reliability Assessments

A subset of each central PyL imaging readers' scans will be evaluated twice, after a washout period of at least four weeks. The test-retest reliability of each reader will be assessed by calculating percent agreement (concordance) and Cohen's pairwise kappa and its respective 95% confidence interval for the dichotomous results (positive or negative) for all subjects with two scan interpretations.

The agreement between the three independent readers will be assessed by calculating percent pairwise concordances and Fleiss's overall multi-assessor kappa and its respective 95%

confidence interval will be calculated for the dichotomous result (positive or negative) for each scan across all subjects.

The agreement between the each of three independent readers and the local site reader will be assessed by calculating percent concordance and Cohen's pairwise kappa and its respective 95% confidence interval for the dichotomous results (positive or negative) across all subjects.

8.6. Safety Analysis

8.6.1. Adverse Events

Adverse events are captured from the time of ^{18}F-DCFPyL administration until the scheduled safety follow-up telephone call scheduled between 5 and 11 days after dosing. All adverse events are considered treatment-emergent. Adverse events will be coded using MedDRA. The severity of each adverse event will be rated using the CTCAE 5-point scale.

8.6.1.1. Summaries of Adverse Event Incidence Rates for All Subjects

The incidence and percentage of subjects reporting a treatment-emergent AEs (TEAEs) will be summarized by MedDRA SOC and Preferred Term. If a subject reports more than one adverse event with the same preferred term, the subject will be counted once with the highest severity. Subject listings will be prepared for all adverse events, all serious AEs, all AEs leading to study discontinuation and for all deaths.

An overall summary will be prepared that presents:

- the number and proportion of subjects reporting TEAEs
- the number and proportion of subjects reporting a treatment-related TEAEs
- the number and proportion of subjects reporting TEAEs CTCAE grade 3 and above
- the number and proportion of subjects reporting TEAEs leading to study discontinuation
- the number and proportion of subjects reporting serious TEAEs, both fatal and non-fatal

Summary tables will be created for:

- the incidence, presented as the number and percent of subjects, for all TEAEs by MedDRA SOC and PT, with all relationships to study drug and severity ratings combined
- the incidence, presented as the number and percent of subjects, for all TEAEs by MedDRA SOC and PT, with all relationships to study drug and severity ratings combined, reporting only TEAEs with incidence > 5%.
- the incidence of all TEAEs by MedDRA SOC and PT for events considered related to study drug
- the incidence of all TEAEs by MedDRA SOC and PT for events by severity as expressed by CTCAE grade.

8.6.1.2. Handling of Missing and Partial AE Onset and Stop Dates

In this study, the subjects are followed up for approximately one week (±3 days) for the onset of adverse events. All efforts will be made to avoid missing start dates. If an adverse event has a stop date prior to the safety follow-up telephone call, it is expected to have a complete date. If the event is ongoing at the time of the follow-up call, then the stop date will not be recorded. If any event has a partial start date or stop date, it will be included in the analysis of adverse events and will be considered treatment-emergent. There is no planned imputation to account for incomplete dates.

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

The incidence of all serious AEs by MedDRA SOC and PT will be summarized by the number and percent of subjects. Similarly, the incidence of all AEs leading to study discontinuation and all deaths will be presented by MedDRA (SOC) and (PT) as summary tables.

8.6.2. Study Drug Exposure and Compliance

Each subject will receive a single intravenous injection of ^{18}F-DCFPyL. Exposure to ^{18}F-DCFPyL will be summarized by administered activity in mCi and volume administered in mL. The table will include the number of subjects dosed and descriptive statistics for the injection volume administered in mL and activity in mCi. A listing of drug administration will include each subject's date of administration, volume administered, and activity delivered.

8.6.3. Concomitant and Other Medications

Concomitant medications are medications taken by the subject after dosing with study drug until the end of follow-up for each subject. Medications that are ongoing at the time of dosing will also be included as concomitant medications. Medications will be coded using the WHO drug dictionary. All recorded medications will be summarized by ATC level 4 category and preferred term and presented as number and percentage of subjects in the safety population. If a subject has a specific medication recorded more than once, it will only be counted once. A subject listing will present all recorded concomitant medications, dates of administration and timing relative to dosing.

8.6.3.1. Handling of Missing and Partial Concomitant and Other Medication Start and Stop Dates

All medications are to be recorded as of the day of dosing and until the end of follow-up for the subject. All new medications are expected to have complete start dates. All medications discontinued while the subject is participating in the study should also have complete end dates. Any ongoing medications at the end of the subject's participation will not have a stop date. Medications that were ongoing at the time of subject dosing will be allowed incomplete dates if a start year is recorded. These medications will be treated as baseline medications. To calculate time since discontinuation of ADT to study entry, the15th of the month will be substituted for missing day of the month, July will be substituted for missing month, and July 1 will be substituted for missing day and month. If the entire stop date for prior ADT use is missing, the date will be considered missing.

8.6.4. Laboratory Data

Only serum PSA will be assessed in this study. No other laboratory parameters are required. PSA will be an analyzed by a central laboratory. The baseline value is required for all subjects in the safety population and will be presented as descriptive statistics. For those subjects undergoing efficacy follow-up who will undergo radiation therapy, PSA will be evaluated every three months until the baseline value decreases by at least 50%, or until the subject is followed for nine months. For those subjects, the PSA values and changes from baseline will be summarized at each post-treatment visit. The number and percent of subjects who achieve the 50% reduction from baseline at each 3-month follow-up visit will be presented as an efficacy endpoint.

8.6.5. Vital Signs

Blood pressure (systolic and diastolic) and heart rate will be measured and recorded prior to study drug dosing and following dosing on study day 1. The recorded values and their respective changes from the pre-dose values will be summarized using descriptive statistics. A subject listing will present the recorded vital signs for each subject.

8.6.6. Physical Examination

Physical examinations are not required in this study. Any relevant physical finding noted at the screening visit will be included in the subject's medical history. Any changes in or new physical findings following study drug administration will be recorded as AEs.

9. DERIVED AND TRANSFORMED DATA

9.1.1. Baseline Age

The subject's age in years will be calculated based on date of informed consent using the following formula:

Age (years) = FLOOR((date of informed consent – date of birth)/365.25)

where the FLOOR function returns the unrounded integer part of the result.

9.1.2. Study Day

If the date of interest occurs on or after the dosing date, then study day will be calculated as (date of interest – date of dosing) + 1. If the date of interest occurs prior to the dosing date, then study day will be calculated as (date of interest – dosing date). There is no study day 0.

9.1.3. Change from Baseline

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing.

9.1.4. Visit Windows

The visit windows for each study visit are detailed in Table 7.

Table 7: Visit Windows (Days)

Visit	Relative Target Day	Visit Window (Day)
Screening	-30 to 1	-30 to 1
Study drug dosing and Imaging	1	1
Safety phone call	8	5 to 11
Efficacy follow-up (surgery, biopsy or conventional imaging)	2 to 60	2 to 60
PSA month 3 (locoregional RT)	3 months ±7 days after start of RT, which can be on days 2 to 60	85 to 157
PSA month 6 (locoregional RT)	6 months ±7 days after start of RT, which can be on days 2 to 60	115 to 187
PSA month 9 (locoregional RT)	9 months ±7 days after start of RT, which can be on days 2 to 60	145 to 217

10. REFERENCES

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11. APPENDIX

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14.3.1.7	Summary of Drug-Related Treatment Emergent Adverse Events by Severity Grade	Safety	
14.3.2 Listing of Deaths or Other Serious or Significant AEs			
14.3.2.1	Listing of Patient Deaths and/or Discontinuations	Safety	
14.3.2.2	Listing of Serious Treatment Emergent Adverse Events	Safety	
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events			
14.3.4 Laboratory Data			
14.3.4.1	Summary of Values and Changes from Baseline in Serum PSA Data and Study Visit	Safety	

Title		Population	Comments
14.3.5 Vital Signs			
14.3.5.1	Summary of Values and Change from Baseline in Vital Signs from Pre-dosing to Post-dosing	Safety	
14.3.6 Other Safety			
14.3.6.1	Summary of Concomitant Medications	Safety	
14.3.6.2	Summary of Concomitant Procedures	Safety	
14.3.6.3	Summary of Drug Exposure	Safety	

Listings

Title		Population	Comment
16.2. 1 Enrollment and Discontinuation			
16.2.1.1	Subject Enrollment Information	Consented	
16.2.1.2	Subject Disposition	Consented	
16.2.2 Protocol Deviations			
16.2.2.1	Subjects who did not Satisfy Inclusion/Exclusion Criteria	Consented	
16.2.2.2	Protocol Deviations	Safety	
16.2.3 Subjects Excluded from Efficacy			
16.2.3.1	Subjects Excluded from Efficacy Analysis	Safety	
16.2.4 Demographics and Baseline Characteristics			
16.2.4.1	Subject Demographic and Baseline Characteristics	Safety	
16.2.4.2	Medical History	Safety	
16.2.4.3	Historical Prostate Cancer Treatments	Safety	
16.2.4.4	Baseline/Screening Conventional Imaging	Safety	
16.2.5 Compliance and/or Drug Concentration			
16.2.5.1	Study Drug Administration	Safety	
16.2.6 Individual Efficacy Response Data			
16.2.6.1	Primary Efficacy Results	FAS	
16.2.6.2	Central Imaging Reader Results	FAS	
16.2.6.3	Central Imaging Truth Panel Results	FAS	
16.2.6.4	Local Site Imaging Reader Results	FAS	
16.2.6.5	Needle-guided Biopsy	FAS	
16.2.6.6	Surgical Procedures	FAS	
16.2.6.7	Pathology Results	FAS	
16.2.6.8	Correlative Imaging and Local Reader Results	FAS	
16.2.6.9	Locoregional Radiation Therapy	FAS	Subset of FAS with PSA as truth standard
16.2.6.10	Medical Management Questionnaire Results	Safety	
16.2.7 Adverse Event Listings			
16.2.7.1	Adverse Events	Safety	
16.2.8 Listing of Laboratory Results			
16.2.8.1	Serum PSA Data	Safety	
16.2.9 Other Safety			

Title		Population	Comment
16.2.9.1	Vital Sign Data	Safety	
16.2.9.2	Concomitant Medications	Safety	
16.2.9.3	Concomitant Procedures	Safety	