CLINICAL STUDY PROTOCOL

Study Number	1095-2301
Study Title	**A** multicenter, **R**andomized, controlled phase 2 study: Efficacy and safety of I-131-1095 **R**adiotherapy in combination with enzalutamide in metastatic castration-resistant pr**O**state cancer (mCRPC) patients **W**ho are ^{18}F-DCFPyL prostate-specific membrane antigen (PSMA)-avid, chemotherapy-naïve, and progressed on abiraterone **(ARROW)**
Product Name	I-131-1095
Regulatory Agency Identifying Number(s)	IND 140447 (FDA); HC6-024-E223364 (Health Canada)
Sponsor	Progenics Pharmaceuticals, Inc. 331 Treble Cove Road Building 300, 2nd floor N. Billerica, MA 01862 978-667-9531
Protocol Version & Date	Original: 05 Dec 2018 Amendment 1: 06 Feb 2019 Amendment 2: 22 Aug 2019 Amendment 2.1: 02 Oct 2019 Amendment 2.2: 25 Nov 2019 Amendment 3: 23 April 2021 Amendment 4: 28 Feb 2022 Amendment 5: 29 Jun 2023

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

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Protocol Version & Date	Amendment 5: 29 June 2023

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

April Teitelbaum 29 June 2023

April Teitelbaum, MD, Medical Monitor

DocuSigned by:
nand kishore rawat
29-Jun-2023 | 12:00 EDT
Signer Name: nand kishore rawat
Signing Reason: I approve this document
Signing Time: 29-Jun-2023 | 12:00 EDT
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Nand Kishore Rawat, PhD, Director, Biostatistics

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29-Jun-2023 | 17:28 EDT
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Iryna Teslenko, MD, Vice President, Clinical Development

INVESTIGATOR'S AGREEMENT

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

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

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

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

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

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

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

_____

Signature of Principal Investigator

_____

Printed Name of Principal Investigator

_____

Date (dd-MMM-yyyy)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Email and Telephone Number
Clinical Study Lead	Angel Koo	Email: angel.koo@lantheus.com Phone: 978-671-8902
Medical Monitor and Drug Safety Physician	April Teitelbaum	Email: april.teitelbaum@lantheus.com Phone: (609)369-2237

2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Progenics Pharmaceuticals, Inc.</td></tr>
<tr><td colspan="2">Investigational Products (IPs): I-131-1095 and ^{18}F-DCFPyL (PyL)</td></tr>
<tr><td colspan="2">Protocol Number: 1095-2301</td></tr>
<tr><td colspan="2">Title of the Study: A multicenter, Randomized, controlled phase 2 study: Efficacy and safety of I-131-1095 Radiotherapy in combination with enzalutamide in metastatic castration-resistant prOstate cancer (mCRPC) patients Who are ^{18}F-DCFPyL prostate-specific membrane antigen (PSMA)-avid, chemotherapy-naïve, and progressed on abiraterone (ARROW)</td></tr>
<tr><td colspan="2">Phase: 2</td></tr>
<tr><td colspan="2">Number of Study Centers: Approximately 30 sites</td></tr>
<tr><td colspan="2">Number of Subjects (planned): Approximately 120 subjects (80 subjects to receive I-131-1095 plus enzalutamide versus 40 subjects to receive enzalutamide alone)</td></tr>
<tr><td colspan="2">Study Population: Men with PSMA-avid mCRPC who are indicated to receive enzalutamide following documented progression on abiraterone, and are ineligible or refuse to receive chemotherapy</td></tr>
<tr><td colspan="2">Study period (years):
Approximately 5 years total duration:
Date first subject enrolled: Q2 2019
Date last subject completed for primary endpoint: Anticipated Q3 2023
Date last subject is expected to finish the Long Term Follow up period: Q3 2024</td></tr>
<tr><td>Study Objectives:
Primary Objective: To determine the efficacy of I-131-1095 combined with enzalutamide compared to enzalutamide alone assessed by PSA response rate according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria.

Secondary Objectives:
• To determine the radiographic response of I-131-1095 combined with enzalutamide compared to enzalutamide alone based on PCWG3-modified RECIST 1.1 criteria
• To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on radiographic progression free survival (rPFS) as defined by RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
• To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on overall survival (OS)</td><td>Study Endpoints:
Primary Endpoint: PSA response rate according to PCWG3 criteria defined as the first occurrence of a 50% or more decline in PSA from baseline, confirmed by a second measurement at least 3 weeks later.
Secondary Endpoints:
• Objective response rate (ORR) from Baseline to the final assessment performed for each patient defined as the proportion of patients who have a partial (PR) or complete response (CR) based on RECIST 1.1 for soft tissue or PCWG3 for bone (PCWG3-modified RECIST 1.1)
• rPFS defined as time from randomization to the first occurrence of radiographic progression based on RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
• OS defined as time from randomization to death from any cause</td></tr>
</table>

• To evaluate the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on PSA kinetics • To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on duration of response • To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on time to initiation of any new treatment for prostate cancer	• PSA progression defined as the time from randomization to the date of the first PSA increase from Baseline ≥25% and ≥2 ng/mL above nadir confirmed by a second PSA assessment defining progression ≥3 weeks later per PCWG3 • Duration of response defined as the time from the first date of complete or partial response to the first occurrence of radiographic progression based on PCWG3-modified RECIST 1.1, or protocol defined unequivocal clinical progression. • Time to next treatment defined as the time from randomization to initiation of any new treatment of prostate cancer
Safety Objectives • To determine the safety and tolerability of I-131-1095 combined with enzalutamide	***Safety Endpoints:*** • Incidences of treatment-emergent adverse events and serious adverse events measured by CTCAE v5.0 • Number of subjects discontinuing study drug due to adverse events • Changes from baseline in physical exam findings, vital signs, clinical laboratory values, and ECG values • Incidences of concomitant medications over time
Exploratory Objectives • To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on PSMA-avid tumor burden using ^{18}F-DCFPyL PET/CT • To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on symptomatic skeletal events (SSEs) • To evaluate patient reported quality of life outcomes • To determine changes in automated bone scan index (aBSI) from baseline • To determine changes in ECOG performance status from baseline	***Exploratory Efficacy Endpoints***: • ^{18}F-DCFPyL uptake defined as change from baseline in SUV_{max} and lesion counts to each study defined timepoint • Time from randomization to first SSE defined as symptomatic fracture, radiation or surgery to the bone, or spinal cord compression • Rate of pain progression, defined as an increase of ≥30% from baseline in the Brief Pain Inventory Short Form (BPI-SF) pain intensity score at 6 months • Overall and component scores of the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire • SF-12v2 domain scores, Physical Component Summary (PCS) scores and Mental Component Summary (MCS) scores • Summary statistics for EQ-5D-5L VAS • Summary statistics for EQ-5D-5L Index • aBSI scores • ECOG performance status

Study Design

This study is a multicenter, open label, randomized phase 2 study of I-131-1095 radiotherapy (≤100 mCi/dose every 8 weeks for up to four doses) in combination with enzalutamide compared to enzalutamide alone in patients with progressive metastatic castration-resistant prostate cancer (mCRPC). Patients must have documented progression on abiraterone and be indicated for treatment with enzalutamide. Patients must not have had prior treatment with taxane-based chemotherapy for castration-resistant prostate cancer (CRPC) and must be ineligible or refuse to receive chemotherapy at time of consent. Enzalutamide will be prescribed per approved labeling.

Approximately 120 subjects at approximately 30 sites in the United States and Canada will be centrally randomized in a 2:1 ratio (80 subjects to receive I-131-1095 plus enzalutamide versus 40 subjects to receive enzalutamide alone); randomization will be stratified by protocol-defined risk group (intermediate vs. high risk prostate cancer). See Section 7.4 for detailed definition).

Subjects will undergo PSMA imaging with ^{18}F-DCFPyL PET/CT as part of Screening to confirm high PSMA expression, as evaluated by central review.

Safety data will be monitored during the Randomized Treatment Period on an ongoing basis by an independent Data Monitoring Committee (iDMC) and the Sponsor. An interim analysis for efficacy will be performed after a minimum of 48 evaluable subjects have prostate-specific antigen (PSA) data for at least 3 months following the first dose of randomized treatment (I-131-1095 or enzalutamide)

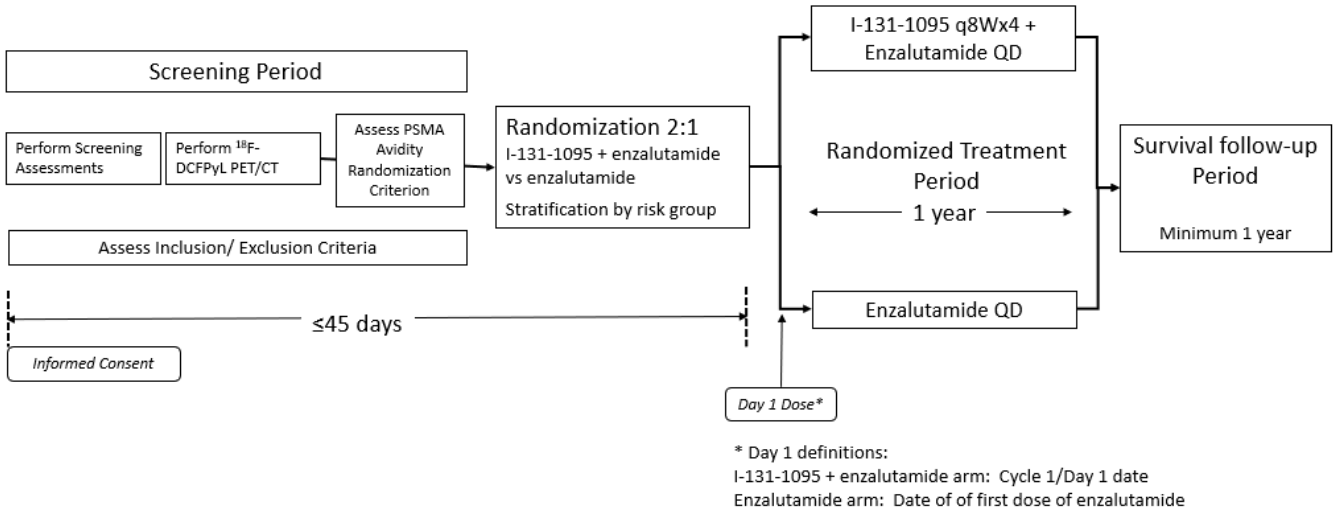
During the Randomized Treatment Period, all subjects will be followed for one year following the first dose of randomized treatment for the following assessments of prostate cancer: PSA, disease status on CT/MR, bone scan and ^{18}F-DCFPyL-PET/CT, automated bone scan index, SSE, survival status, and patient reported outcomes (PROs). The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) and the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria will be used by investigators to determine radiologic response and clinical and radiographic disease progression.

Safety and tolerability will be assessed by the collection of treatment-emergent AEs, monitoring of vital signs and physical examinations, safety laboratory tests, and ECGs.

Subjects may discontinue early from the Randomized Treatment Period but may choose to enter the Survival Follow-up Period as described below, to be followed for survival status.

Following the Randomized Treatment Period, patients will enter the Survival Follow-up Period during which survival data, adverse events of special interest (AESIs) and new anti-cancer therapy will be collected via phone call visits for at least one year or to the end of the study (whichever is later). following completion or early discontinuation of the Randomized Treatment Period.

Study Schema



Study Duration:

Subjects who provide informed consent will have up to 45 days to complete all screening procedures to assess eligibility criteria. Within the 45-day screening period, subjects who are expected to meet all eligibility criteria will receive ^{18}F-DCFPyL and PET/CT to assess the randomization criterion of PSMA avidity. If subjects do not advance to being randomized into the study and are deemed as a screen failure, their total study duration is estimated to be up to 45 days.

Subjects who meet all eligibility and randomization criteria will be randomized (2:1) to receive I-131-1095 plus enzalutamide or enzalutamide alone. Day 1 is defined as the date a subject receives the first dose of their randomized treatment. In the case of subjects randomized to the I-131-1095 + enzalutamide arm, Day 1 will be the date they receive I-131-1095 as part of Cycle 1/Day 1. For subjects randomized to the enzalutamide arm, their respective Day 1 is defined as the date they receive their first dose of enzalutamide. Following Day 1, study subjects have scheduled follow-up visits in the Randomized Treatment Period up to 12 months after their first dose of I-131-1095 and/or enzalutamide. The Randomized Treatment Period is comprised of approximately 20 visits, including up to four I-131-1095 dosing cycles (16 visits) with a dosimetry assessment prior to the third dosing cycle, and four additional safety/efficacy visits including an End of Treatment visit. A Dosing Cycle is defined as an 8-week period starting with Day 1 of randomized dosing. The start of a Dosing Cycle corresponds with the day of study drug administration for subjects receiving I-131-1095. A delay in dosing beyond the 8-week cycle is permitted up to an additional 6 weeks, or as agreed upon with prior approval from the study Medical Monitor.

Subjects may discontinue from the Randomized Treatment period at any time prior to reaching the Week 53/EOT Timepoint. Subjects who discontinue prematurely from the Randomized Treatment period or complete the full Randomized Treatment period per-protocol are given the option to enter the Survival Follow-up Period during which survival data, adverse events of special interest (AESIs) and new anti-cancer therapy will be collected via phone call visits every 13 weeks for at least one year or to the end of the study (whichever is later) following completion or early discontinuation from the Randomized Treatment Period). The end of study is defined as the

timepoint when the last patient completes the 1-year timepoint in the Survival Follow-up Period (Week 105). As such, the maximum duration a patient may participate in the study is approximately 5 years.

IP Doses and Mode of Administration:

There are two investigational products (IPs) in this study:

1) ^{18}F-DCFPyL (PyL) for the imaging of prostate cancer lesions will be administered to all subjects prior to randomization to confirm PSMA avidity, at Week 7, and at the End of Treatment Visit. PyL is supplied to each institution on the planned day of administration in a unit-dose syringe (contained in a lead shield unit-dose system) with no additional preparation required for a 9 mCi (333 MBq) unit dose.

2) I-131-1095 for the PSMA-targeted treatment of prostate cancer will be administered following randomization. Each shielded vial containing I-131-1095 will be shipped frozen at -70ºC and should be stored at ≤ -70ºC or thawed for immediate use. Each vial will contain approximately 200 mCi of I-131-1095 at Time of Calibration (TOC). Aseptic procedures are to be used during withdrawal of study radiopharmaceutical for IV administration of a prescribed dose up to 100 mCi.

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for this study:

1. Male ≥ 18 years of age
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features at initial diagnosis
3. Castration-resistant prostate cancer, with serum testosterone ≤ 50 ng/dL (1.73 nM) at Screening
4. Metastatic disease documented by bone lesions on whole body bone scan or soft tissue lesions measurable per RECIST 1.1 on CT/MRI prior to Randomization or up to 21 days prior to Screening
5. Evidence of disease progression on prior abiraterone therapy. Disease progression is defined by meeting at least one of the following criteria:
    a. PSA progression as defined by a minimum of two rising PSA levels at least 1 week apart
    * *Distinct from PCWG3 criteria which is used for the determination of PSA progression for study purposes following randomization*
    b. Soft tissue disease progression* defined by RECIST 1.1
    c. Bone disease progression* defined by two or more new lesions on bone scan
    **For subjects enrolling on the basis of soft tissue or bone progression, the baseline scan must show progression relative to a comparison scan performed during prior abiraterone therapy or after discontinuation from abiraterone. If the comparison scan is not available, the baseline scan report must reference the previous scan to document progression*
6. Planned for treatment with enzalutamide
7. Subjects who are ineligible or choose not to receive taxane-based chemotherapy based on personal preference or physician opinion. Examples of conditions that could make a patient ineligible or refuse to receive taxane-based chemotherapy, but would allow them to still be eligible to receive I-131-1095 include the following:
    a. Poor performance status
    b. Prior intolerance to cytotoxic agents
    c. History of another malignancy suspected for recurrence or metastases
    d. Other serious medical conditions such as symptomatic peripheral neuropathy CTCAE Grade 2 or higher; or clinically significant cardiovascular disease per the Investigator or treating physician

8. Subjects receiving bisphosphonates must have been on stable doses for ≥ 4 weeks prior to Randomization
9. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
10. If sexually active, agree to use a medically acceptable method of birth control (e.g., spermicide in conjunction with a barrier such as a condom) or sexual abstinence from the time of dosing through 28 days after the last dose of I-131-1095. Sperm donation is prohibited from the time of dosing through 28 days after the last dose of I-131-1095. Female partners must use hormonal or barrier contraception unless postmenopausal or abstinent.
11. Estimated life expectancy of at least 6 months as determined by the Investigator or treating physician
12. Able and willing to provide signed informed consent and comply with protocol requirements

Exclusion Criteria:

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

1. Received any anti-tumor therapy within 4 weeks of Randomization, with the exception of abiraterone, gonadotropic-releasing hormone (GnRH) therapy and non-radioactive bone-targeted agents
2. Received prior chemotherapy for castration-resistant prostate cancer (CRPC)
   * Prior taxane based chemotherapy in a hormonal setting is allowed
3. Superscan as evidenced on baseline bone scan (defined as extensive significant uptake demonstrated throughout the axial, proximal and peripheral skeleton system)
4. Treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 within 6 months prior to Randomization
5. Prior hemi-body irradiation
6. Prior PSMA-targeted radioligand therapy
7. Major surgery within 4 weeks of Randomization
8. Impaired organ function as evidenced by the following laboratory values in Screening labs:
   a. Absolute neutrophil count < 1500 µL
   b. Platelet count < 100,000/µL
   c. Hemoglobin < 9.5 g/dL
   d. Albumin < 3.0 g/dL (30 g/L)
   e. Total bilirubin > 2 x ULN unless in instances of known or suspected Gilbert's disease
   f. AST and ALT > 2.5 x ULN
   g. Calculated creatinine clearance (CrCL) < 30 mL/min (Cockroft-Gault equation), or currently on renal dialysis
9. QT interval corrected for heart rate (QTc) >470 msec during Screening
10. Previous use of enzalutamide for >7 days prior to consent
11. Planned initiation of alternative therapy for prostate cancer, investigational therapy, or participation in clinical trials during the study
12. History or risk of seizure (i.e., clinically significant neurological disorder) or any other condition that contraindicates treatment with enzalutamide (Xtandi®) as per the package insert
13. Gastrointestinal disorder affecting absorption of oral medications
14. Known or suspected brain metastasis or active leptomeningeal disease
15. Active malignancy other than prostate cancer, with the exception of curatively treated non-melanoma skin cancer, carcinoma in situ, or non-muscle invasive bladder/urothelial cancer
16. Active urinary incontinence

17. Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise obtaining reliable data, achieving study objectives, or completing the study

Randomization Criterion:

Subjects must also be screened for ^{18}F-DCFPyL avidity as defined by the below criteria to proceed to Randomization:

- ^{18}F-DCFPyL PET/CT imaging shows significant PSMA uptake (SUVmax > 1x liver SUVmean) in all prostate cancer lesions, except as noted below:
  - PSMA negative soft tissue lesions < 1.0 cm in short axis;
  - PSMA negative lymph node lesions < 1.5 cm in short axis;
  - PSMA negative bone lesions with a soft tissue component < 1.0 cm in short axis or without a soft tissue component of any size

Assessments:

Subjects that initiate randomized treatment with enzalutamide alone or in combination with I-131-1095 will be followed for one year following the first dose of treatment for the following assessments of prostate cancer: PSA, disease status on CT/MR, bone scan and ^{18}F-DCFPyL PET/CT, aBSI, SSEs, survival status and patient reported outcomes (PROs). Subjects will also be evaluated for unequivocal clinical progression.

Safety and tolerability will be assessed by collecting treatment-emergent adverse events, vital signs, physical examinations, concomitant medications and 12-lead ECGs. Clinical laboratory tests will also be conducted.

Survival data, adverse events of special interest and new anti-cancer therapy will be collected via phone call visits for at least one year following completion or early discontinuation of the Randomized Treatment Period until the end of the study (whichever is later).

Statistical Methods:

Analysis Populations:

- **Full Analysis Set (FAS)**

The FAS is defined as all randomized subjects and will be analyzed according to the treatment group as randomized. The FAS will be used for all efficacy analyses and baseline parameters; the primary efficacy conclusion will be based on the result of this analysis.

- **Per-Protocol (PP) Set**

The PP Set will consist of the FAS excluding subjects with major protocol violations, subjects who did not receive at least one dose of study treatment or who did not complete at least one post-baseline PSA assessment. If a subject received at least 1 dose of I-131-1095 then the subject is assigned to the I-131-1095 group, otherwise treatment assignment is per the randomization. The PP analysis of the primary endpoint will be used as one of the sensitivity analyses.

- **Safety Set**

The safety set is defined as all subjects who received any dose of study drug defined as ^{18}F-DCFPyL, I-131-1095 and enzalutamide. Subjects will be analysed according to the treatment received. Any subject who received any amount of I-131-1095 will be assigned to the I-131-1095 treatment group. The safety set will be used for the safety and baseline parameters. The safety set will be used for the safety and baseline parameters.

Statistical Analyses:

Efficacy:

- **Primary Endpoint Analyses**

The analysis of the primary endpoint will be performed using a 2-sided Cochran-Mantel-Haenszel chi-squared test based on the FAS population stratified by risk category (intermediate vs high-risk) to compare the two treatment groups in PSA reduction of at least 50% from baseline as confirmed by a second PSA measurement at least 3 weeks later.

A sensitivity analysis based on 2-sided chi-squared test will be performed on PSA reduction of at least 50% from baseline confirmed at any point after the first reduction. The primary endpoint results will also be confirmed in a sensitivity analysis based on PP set.

In general, if more than 20% of the expected cell frequencies are less than 5, then a Fisher's exact test will be performed in place of the Chi-squared test.

- **Secondary Endpoint Analyses:**

All secondary endpoints will be analyzed for the FAS Set.

The endpoint of overall response rate will be analyzed using a 2-sided chi-squared test to compare the proportions between treatment groups based on a type I error of 0.05. If more than 20% of the expected cell frequencies are less than 5, then a 2-sided Fisher's exact test will be performed.

The following secondary endpoints will be analyzed using a 2-sided log rank test stratified by risk category (intermediate vs high-risk) to compare the two groups. Kaplan-Meier plots will also be presented along with median survival times between treatment groups and 2-sided 95% confidence intervals.

- OS defined as time from randomization to death
- PSA progression defined as time from randomization to date of first confirmed PSA progression value.
- rPFS defined as time from randomization to the first occurrence of radiographic progression based on RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
- Duration of response defined as time from first date of CR or PR to date of disease progression
- Time to next treatment defined as the time from randomization to initiation of any new treatment for prostate cancer

- **Exploratory Endpoint Analyses:**

All exploratory protocol-defined endpoints will be analyzed based on for the FAS set.

The rate of pain progression defined from BPI-SF will be analyzed using a 2-sided chi-squared test to compare the two treatment groups based on a type I error of 0.05. If more than 20% of the expected cell frequencies are less than 5, then a 2-sided Fisher's exact test will be performed.

The following continuous endpoints will be transformed where applicable and analyzed using repeated measures analysis of variance to evaluate the difference between treatment groups. If normality cannot be assumed within each treatment group per the Shapiro-Wilks test or the responses have an ordinal scale; a generalized model will be used.

- ^{18}F-DCFPyL uptake defined by SUV_{max}

- ^{18}F-DCFPyL positive lesion counts
- Overall score from FACT-P
- The physical domain from FACT-P
- The social/family domain from FACT-P
- The emotional domain from FACT-P
- The functional/well-being domain from FACT-P
- The SF-12v2 Physical Component Summary (PCS) score
- The SF-12v2 Mental Component Summary (MCS) score
- aBSI scores
- ECOG performance status

Time from randomization to first symptomatic skeletal event (SSE) will be analyzed using a stratified 2-sided log-rank test to compare the differences between groups.

EQ-5D-5L VAS and index values will be compared between treatment groups.

Safety:

- **Safety Analyses**

All safety endpoints will be presented for the safety set and summarized by treatment group. Tabular summaries will include the incidence overall (number and percentage of patients with events classified by system organ class and preferred term) as well as incidence by intensity, causality, and outcome (e.g. leading to discontinuation of study drug).

Patients with the same adverse event reported more than once will be counted once at the maximum severity or strongest relationship to study drug.

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

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Definition of Terms

Abbreviation or Specialist Term	Explanation
aBSI	Automated bone scan index
ADME	Absorption, Distribution, Metabolism, Excretion
ADT	Androgen deprivation therapy
AE	Adverse event
AESI	Adverse Event of Special Interest
AR-V7	androgen-receptor splice variant 7 messenger RNA
BPI-SF	Brief Pain Index- Short Form
CFR	Code of Federal Regulations
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQol Group health-related quality of life assessment
FACT-P	Functional Assessment of Cancer Therapy- Prostate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GnRH	Gonadotropin Releasing hormone
Hct	Hematocrit
HED	Human equivalent dose
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	Independent Data Monitoring Committee
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
ITT	Intention-to-treat

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
mCi	Millicurie
mCRPC	Metastatic castration-resistant prostate cancer
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
NAAD	Novel anti-androgen drug
NLCB	No Longer Clinically Benefiting
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetic
PRO	Patient-reported outcome
PSA	Prostate specific antigen
PSMA	Prostate-specific membrane antigen
PT	Preferred Term
PyL	^{18}F-DCFPyL
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
ROI	Regions of interest
rPFS	Radiographic progression-free-survival
SAE	Serious adverse event
SF-12	12-Item Short Form Health Survey
SOC	Standard of Care
SPECT	single-photon emission computed tomography
SSE	Symptomatic Skeletal Event
SUV_{max}	Maximum Standardized Uptake Value
$t_{1/2}$	Half-life
TSH	Thyroid stimulating hormone
TEAE	Treatment-emergent adverse event
US	United States
VAS	Visual Analogue scale
VOI	Volumes of interest
WBC	White blood cell count
WHO	World Health Organization

5. INTRODUCTION

5.1. Metastatic, Recurrent Prostate Cancer

Prostate cancer is the most common cancer among men in the USA with an estimated number of new cases of 174,650 annually; it also represents the second most common cause of cancer-related death in men.[1] The vast majority of men dying of prostate cancer succumb to metastatic, recurrent disease. Hormonal therapy remains a first-line treatment for metastatic prostate cancer. Initial response to hormonal therapy with chemical or surgical castration is effective; however, most patients will progress to a castration-resistant phase of the disease within 2-3 years of initiation.[2] In recent years, novel anti-androgen drugs (NAADs) such as abiraterone, a steroidal androgen synthesis inhibitor, and enzalutamide, a nonsteroidal androgen receptor blocker, have shown significant survival benefits in metastatic castration-resistant prostate cancer (mCRPC) patients compared to prior standard of care, by approximately 4 and 5 months, respectively, regardless of status of prior treatment with taxane-based chemotherapy.[3, 4, 5] Despite the demonstrated benefit of these agents, not all patients with CRPC are responsive to NAAD treatment and the disease will continue to progress. With the current prevalent use of NAAD in mCRPC patients and the increased occurrence of NAAD resistance[6], there is an urgent medical need for an effective therapeutic option for these patients with a modality of novel mechanism of action that could potentially overcome NAAD resistance.

5.2. Prostate-Specific Membrane Antigen (PSMA)

PSMA, also known as folate hydrolase I or glutamate carboxypeptidase II, is a trans-membrane glycoprotein primarily expressed in normal human prostate epithelium at very low levels, if at all, but is upregulated in prostate cancer, including metastatic disease.[7] PSMA is expressed by virtually all prostate cancers and its expression is further increased in poorly differentiated, metastatic and hormone-refractory prostate cancers, rendering it a useful diagnostic and therapeutic target in these patients.[8]

Radiotherapy using PSMA targeting moieties combines the favorable targeting properties of these agents with the biological effects of high linear energy transfer radiation as is seen with alpha- and beta-emitting particles. Another advantage is the targeted delivery of a very low quantity of the compound allows for dosing with a favorable safety profile compared to commonly used anti-cancer therapies, such as chemotherapy. PSMA has also proven to be a promising target for imaging diagnostics offering the ability to assess avidity and/or biodistribution information prior to targeted radionuclide therapy.

Advanced prostate cancer is an attractive target for radionuclide therapy due to the prostate being a non-vital organ, thereby allowing targeting of tissue specific antigens and the combination of circulating biomarkers (e.g. prostate specific antigen [PSA]), molecular imaging techniques including PSMA Positron Emission Tomography (PET), and anatomical imaging to assess therapeutic effects.

Radiotherapy using PSMA has demonstrated promising results. For example, the PSMA radionuclide, 177-lutetium-J591, a beta-emitting monoclonal antibody, was well-tolerated with reversible myelosuppression, and demonstrated anti-tumor activity in patients with progressive mCRPC.[9] Their study provided important preliminary evidence of the safety and efficacy for the use of systemic radiotherapy with PSMA-targeting agent and paved the way for trials with small molecule-PSMA radiotherapy.[10] Small molecule 177-Lu-PSMA agents have also been explored in small retrospective studies. In a recent review of the 177-Lu-PSMA literature, approximately 30-80% of heavily pretreated men with mCRPC achieved ≥50% PSA reduction, which was comparable to the biochemical response

seen with chemotherapy.[11 12] PSMA radiotherapy with alpha-emitting isotopes such as actinium-225 also have been explored in small compassionate use protocols. A case series (n=14) was recently published showing PSA decline in 4 of 9 patients who had progressed after multiple hormone and chemotherapy regimens.[13] Hematological adverse effects were well-tolerated; however, 4 patients discontinued because of severe xerostomia.[13]

5.3. I-131-1095

I-131-1095 is a novel PSMA targeted small molecule currently under development by Progenics Pharmaceuticals, Inc. for the treatment of metastatic prostate cancer. The presence of iodine-131, a beta particle emitting radionuclide, permits I-131-1095 to specifically destroy prostate cancer cells. I-131-1095 binds to the extracellular domain of PSMA selectively with high affinity, and is internalized by prostate cancer cells, allowing absorption of the intense energy emitted by iodine-131 in the cells resulting in targeted cell death. Thus, I-131-1095 is a potential therapeutic option for the treatment of patients with mCRPC. Furthermore, the use of iodine-131 has potential advantages over lutetium-177:

1. Slightly longer range and higher energies that could prove beneficial in larger lesions with incomplete or weak target (PSMA) expression.
2. Broad availability of and well-established risk management plans for I-131 which is commonly used to treat thyroid disease.

5.3.1. Pharmacology

Preclinical data with I-131-1095 have shown high and prolonged tumor uptake along with rapid washout from normal tissues, including the kidneys, resulting in a favorable tumor to kidney discrimination, thus yielding a lethal radiation dose to the tumor while minimizing normal tissue exposure.

5.3.2. Nonclinical Pharmacokinetics, Metabolism and Toxicology

In vivo studies were performed including analysis of the pharmacokinetics, absorption, excretion, metabolism and metabolic profile of I-131-1095 in blood and urine following intravenous administration to Sprague-Dawley rats, and beagle dogs. *In vitro* studies include an assessment of hepatic metabolism, cytochrome p450 induction and inhibition, P-gp interactions and plasma protein binding.

Two single-dose toxicology studies were conducted, one in rats using 1095 alone and one in dogs using 1095 combined with 1111, the non-halogenated analogue of I-131-1095 present in the drug product. The dose levels in the rat study were 32-, 102-, or 312-fold human equivalent dose (HED). Dose levels in the dog study were 361-, 1065-, or 3463-fold HED. Assessment of toxicity in both studies was based on mortality, clinical signs, clinical and anatomic pathology, and toxicokinetic evaluations. All animals survived to their respective sacrifice date in both studies, with no obvious or adverse effects on clinical and pathology testing.

Two repeat-dose toxicity studies were conducted, one in rats and one in dogs, both using 1095 combined with 1111. The dose levels in the rat study were 543-, 1613-, or 2511-fold HED. Dose levels in the dog study were 361-, 1065-, or 3463-fold HED. In both studies, all animals received daily intravenous injections for 28 days, and assessment of the reversibility, persistence, or delayed occurrence of any effects was performed in a subset of animals that were followed for an additional 28-day recovery period. All animals survived to their respective sacrifice date in both studies, with no obvious or adverse effect on clinical and pathology testing.

Three genotoxicity studies of 1095 combined with 1111 were conducted. One study was to evaluate the potential of 1095/1111 to form mutations or to elicit DNA damage. The other two studies were to evaluate the potential of 1095/1111 to damage or induce aberrations in chromosomes. 1095/1111 was negative in the Bacterial Reverse Mutation Assay (tested up to 5000 µg/plate) and did not induce chromosomal aberrations in cultured human peripheral lymphocytes (at dose levels up to 500 µg/mL ± S9 metabolic activation).

Further information can be found in the Investigator's Brochure (IB).

5.3.3. Summary of Relevant Clinical Experience

The tolerability, pharmacokinetics, biodistribution, and dosimetry of radiolabeled 1095 were studied in a phase 1 study (MIP-TX-P101) in seven patients with advanced prostate cancer. Patients were intravenously administered 10 mCi of I-123-1072 and I-123-1095 two weeks apart in a randomized crossover trial design. Both radiolabeled compounds were well tolerated; six mild adverse events (AEs) were reported and no drug-related serious adverse events (SAEs) occurred. Clinical laboratory and ECG results were unremarkable, with no marked differences between the two study compounds. As expected at these imaging doses, thyroid function tests showed no marked or consistent changes with either I-123-1072 or I-123-1095. To examine the effects of thyroid blocking with inorganic iodide prior to injection with I-123-1072 or I-123-1095, mean thyroid radiation exposure for subjects having the thyroid blocked was compared with thyroid radiation exposure in subjects with unblocked thyroid. Mean radiation doses to unblocked thyroid were higher as expected. Specifically, with I-123-1072 the unblocked absorbed dose of 5.4 mGy/MBq compared with 2.3 mGy/MBq for blocked thyroid; for I-123-1095, mean radiation dose to unblocked thyroid was 87 mGy/MBq, compared with 14 mGy/MBq for blocked thyroid. Based on these data, patients who receive a typical diagnostic dose of either of these study radiopharmaceuticals are not expected to be at risk for adverse effects on the thyroid but thyroid blocking at therapeutic doses is warranted.

In addition, preliminary safety of I-131-1095 in mCRPC patients has been shown in an investigator-initiated phase 1 study (NCT03030885) in the US. None of the patients who received therapeutic doses (50 mCi [n=3] and 75 mCi [n=2]) in the phase 1 study experienced any dose-limiting toxicities (DLTs) or any severe or SAEs. All reported treatment-emergent AEs were mild to moderate (CTCAE v4.03 Grade 1-2) in severity. Clinical laboratory results and physical examinations revealed no clinically relevant changes from the pre-dose to post-dose study period. ECGs were performed prior to and following imaging and therapeutic dosing, and results have been clinically unremarkable as of October 2018. Efficacy estimates from these cohorts are not available given the small number of subjects tested as of October 2018.

Furthermore, safety and efficacy data from 34 progressive mCRPC patients treated with I-131-1095 as last-line therapy is available from a compassionate use clinical setting in Germany.[14, 15] No clinically relevant hematologic toxicities were observed in the majority of the patients. WHO CTC grades 1-3 hematologic toxicities were less prevalent but presented in a higher percentage of patients with increased number of therapies. No significant changes in pre- to post-dosing laboratory values for liver enzymes, serum creatinine or thyroid parameters were observed. Xerostomia occurred more frequently in patients with a greater number of mCRPC therapies; most cases (60-70%) were grade 1 or 2 in severity. In regard to efficacy, 70% of patients had a PSA decline of ≥50% after the first therapeutic dose of I-131-1095 therapy.[14] The median overall survival of the patients after the first therapy was 17 months.

Median time to PSA progression was 75 days after the first therapeutic administration, 50 days after the second, and 42 days (n=1) after the third therapeutic dose.

5.3.4. I-131-1095 Rationale for Dose Selection

Based on the available data and with added safety precaution, a 2-tiered dosing approach will be implemented for this phase 2 study. The initial (first) therapeutic dose of I-131-1095 will be set at 100 mCi, as the safety of this single dose is adequately supported by:

1. Available clinical data[15] indicate that an administered dose of I-131-1095 at 100 mCi would result in critical organ exposures well below the maximum estimated dose based on the limit listed in IRCP Publication 118[16] for each of the subjects evaluated.
2. Dosimetry findings from the phase 1 study with I-131-1095 therapy at Memorial Sloan-Kettering Cancer Center in patients with heavily pretreated PSMA-avid mCRPC showed that the estimated maximum dose levels of I-131-1095, without exceeding the ICRP critical organ safe limits, ranged from 248 mCi to 533 mCi. These dosimetry data provide confidence that a subject could safely receive up to a cumulative dose of 200 mCi (or two therapeutic doses of up to 100 mCi each). However, dosimetry assessment for subjects randomized in the I-131-1095 treatment arm must be performed to ascertain critical organ exposure prior to the administration of additional therapeutic dose(s) in this phase 2 study.
3. Experience from a German compassionate use study demonstrated that I-131-1095 therapy with doses up to 200 mCi was well tolerated with no clinically significant hematologic events or other DLTs observed in mCRPC patients[14].
4. Experience from thyroid cancer where standard ablation therapy uses doses of I-131 in excess of 100 mCi has shown an acceptable safety profile.
5. No chemical toxicity from the nonradioactive 1095 molecule is anticipated at the low dose to be administered (~18 µg/ therapeutic dose).

In this study, the Randomized Treatment Period consists of up to four therapeutic dosing cycles (therapeutic dose at 75 or 100 mCi each). Prior to the third therapeutic dose (Cycle 3), subjects will be required to undergo dosimetry assessment (with 10 mCi dosimetric dose of I-131-1095) to determine if additional therapeutic doses may be administered. The doses and patient eligibility for the subsequent cycles will be determined and/or adjusted, if needed, for each patient based on a central dosimetry evaluation. The maximum cumulative dose per patient will be calculated by the central dosimetrist and the total number of cycles will be determined accordingly and approved by the Sponsor before administering doses subsequent to Cycle 2. (see Section 9.2.2.6).

Throughout this document, the term "dose" is meant to denote the amount of radioactivity administered to a patient (mCi). The resulting energy absorbed by various organ and tissues will be referred to as absorbed dose (Gy).

5.4. ^{18}F-DCFPyL

^{18}F-DCFPyL Injection is a novel, radiolabeled small molecule that binds to the extracellular domain of PSMA at high affinity. ^{18}F-DCFPyL Injection was approved on 26 May 2021 by the United States Food

and Drug Administration (US FDA) under the brand name PYLARIFY® (piflufolastat F 18) Injection for PET of PSMA positive lesions in men with prostate cancer:

- With suspected metastasis who are candidates for initial definitive therapy
- With suspected recurrence based on elevated serum PSA level

5.4.1. Pharmacology and ADME

A first-in-human, open-label, single-arm, single-site phase 1/2 study was conducted by Johns Hopkins University to evaluate the radiation dosimetry, biodistribution, metabolism, and safety of 9 mCi (331 MBq) ^{18}F-DCFPyL Injection with PET/CT imaging in 10 men with clinically progressive mCRPC. To assess pharmacokinetics, metabolism, and excretion of ^{18}F-DCFPyL, blood samples were evaluated at three time points: 20 minutes post-injection, 90 minutes post-injection, and at the completion of PET scanning (150 minutes post-injection). Urinary excretion was calculated at approximately 110- and 160-min post-injection. No SAEs were reported. There were three AEs reported in nine subjects, all of which were considered not related to study drug.[17]

Analysis of plasma samples by high-performance liquid chromatography (HPLC) up to 173 minutes post-injection demonstrated that all plasma activities were in the form of non-metabolized parent compound. A rapid washout of ^{18}F-DCFPyL-associated activity from the blood pool and significant renal excretion with radiotracer accumulation in the bladder were observed. The only radioactive component detected in plasma samples was unchanged ^{18}F-DCFPyL. Based on PET imaging, the radioactivity detected in the small intestine was associated solely with the intestinal wall, suggesting a lack of fecal excretion.

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

The radiation absorbed doses to radiosensitive organs such as red marrow and gonads were low (0.01 mGy/MBq or less). Highest radiation exposure was observed in kidneys (0.0896 mGy/MBq), followed by the urinary bladder wall (0.0873 mGy/MBq), parotid glands (0.0495 mGy/MBq), and liver (0.0420 mGy/MBq). PSMA-expressing tissues, including the lacrimal, salivary and parotid glands, exhibited moderate radiation absorbed doses (between 0.042 mGy/MBq and 0.027 mGy/MBq).

The effective dose of ^{18}F-DCFPyL was calculated to be 0.0169 mSv/MBq or 5.5 mGy (0.55 rem) for an injection dose of 9 mCi (333 MBq). This dose is less than other commonly used tracers for oncologic imaging such as ^{18}F-FDG.

Quantitative uptake of ^{18}F-DCFPyL in abnormal foci (maximum standardized uptake value (SUV_{max})), were measured across all available PET/CT time points to determine the optimal imaging time point following injection. At approximately 1 and 2 hours, respectively, the highest uptake and lowest background activity were observed suggesting that PET/CT imaging of ^{18}F-DCFPyL as early as one hour post-injection will allow for the full extent of lesions to be evaluated in most patients.

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

5.4.2. Summary of Relevant Clinical Experience with ^{18}F-DCFPyL PET/CT

In part 2 (Phase 2) of the J1418 study, the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to detect areas of local, nodal and/or distant prostate cancer was planned to in 25 patients with clinically localized intermediate or higher risk prostate cancer (clinical stage ≥T2b or GS ≥7 or PSA ≥10 ng/mL) prior to radical prostatectomy with pelvic lymph node dissection (PLND). Areas of intra- and extraprostatic tumor spread identified with ^{18}F-DCFPyL were compared with postop histopathology as the truth standard.

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

Following independent image reads with adjudication, 7 (28%) subjects were confirmed to have ≥1 site of focal radiotracer within the pelvis consistent with N1 disease. This resulted in a sensitivity and specificity of 71.4% (95% CI 29.0−96.3) and 88.9% (65.3−98.6), respectively, for the presence or absence of metastatic prostate cancer. Similar results were found in the packet-level analysis with a sensitivity of 66.7% (29.9−92.5) and a specificity of 92.7% (80.1−98.5).[19] Additionally, the readers determined that 3 (12%) subjects had PET/CT findings consistent with M1a disease (none had M1b or M1c). All 3 of these patients had a detectable PSA level within 6 months of surgery.

In summary, results from the phase 2 portion of study J1418 suggest that ^{18}F-DCFPyL PET/CT may improve preoperative staging in patients with high risk prostate cancer.

Another open-label, single-arm, single-site phase 2 study (J1545) was completed at Johns Hopkins in 50 subjects with an elevated PSA (≥ 0.2 ng/mL) following radical prostatectomy. This study broadly included men with PSA persistence and recurrent prostate cancer after surgery and aimed to: 1) evaluate the safety of ^{18}F-DCFPyL; 2) describe the number and location of putative sites of metastatic disease as determined by ^{18}F-DCFPyL PET/CT; 3) correlate findings on ^{18}F-DCFPyL PET/CT with conventional imaging (bone scan and cross-sectional imaging); and 4) assess treatment response by ^{18}F-DCFPyL PET/CT following six months of standard of care therapy. Recruitment for this study has ended, but the final analysis of the data has not been completed. No SAEs were reported.

Progenics has completed two phase 3 studies in patients with prostate cancer. PyL-2301 (OSPREY) was an open-label, non-randomized, multicenter phase 2/3 study designed to evaluate the safety and diagnostic performance of ^{18}F-DCFPyL PET/CT imaging to determine the presence or absence of metastatic prostate cancer in subjects with at least high-risk prostate cancer who are planned for radical prostatectomy with PLND (cohort A), and subjects with radiologic evidence of local recurrence or new or progressive metastatic disease (cohort B). Three central, blinded, and independent readers evaluated the ^{18}F-DCFPyL scans. Histopathology served as the reference standard to which imaging findings were compared. This study was conducted at 10 sites in the United States and Canada and publication is pending. Results from this study demonstrate that ^{18}F-DCFPyL has been well-tolerated by all dosed subjects; a total of 51 (13.2%) men experienced at least one drug-related adverse event

(dysgeusia [2.6%] and headache [2.3%] being most common). Seven SAEs were reported but none were considered drug-related SAEs[20]. The majority of adverse events (86%) were mild (NCI CTCAE Grade 1). Five subjects (1.3%) experienced treatment-emergent adverse events (TEAEs) that were Grade 3 in severity, none were Grade 4 or 5. In Cohort A, the sensitivity of ^{18}F-DCFPyL PET/CT ranged among the three readers from 30.6-41.9% (lower bound of 95% CI: 19.2-29.7%), with specificities ranging from 96.3-98.9% (lower bound of 95% CI: 93.6-96.0%). Additionally, the PPV and NPV ranged from 78.1-90.5% and 81.4-83.8%, respectively. In patients with metastatic PCa (Cohort B), the values of sensitivity and PPV ranged from 92.9-98.6% (lower bound of 95% CI: 84.0-91.6%) and 81.2-87.8%, respectively[20].

PyL-3301 (CONDOR) was an open-label, non-randomized multicenter phase 3 study designed to evaluate the diagnostic performance of ^{18}F-DCFPyL PET/CT imaging in patients with biochemically recurrent prostate cancer who have baseline negative or equivocal conventional imaging findings. The study initiated in November 2018 and enrolled 208 subjects. The study was conducted at 14 sites in the United States and Canada. Fourteen patients (6.7%) reported at least one adverse event, with headache (4 patients, 1.9%), fatigue (2 patients, 1.0%), and hypertension (2 patients, 1.0%) being the most frequent. Three (1.4%) patients had at least one drug-related TEAE. One patient (0.5%) reported serious adverse events (all Grade 3), which were hypersensitivity (drug related), headache, and paresthesia (both unrelated to study drug). This patient had an extensive history of allergic reactions. No patient had a Grade 4 or a fatal (Grade 5) TEAE or discontinued the study due to a TEAE. Vital sign changes from pre- to post-dose were not clinically significant. Three SAEs were reported by one patient. Only one of them (hypersensitivity – a single Grade 3 event) was assessed as drug-related.

The primary efficacy endpoint was Correct Localization Rate (CLR) at the subject level in the subset of the subjects with positive ^{18}F-DCFPyL scans (n=123 to 137 for the 3 independent central readers) compared with a composite standard of truth (SOT) of histopathology, correlative imaging or PSA response following radiation. The study achieved the pre-specified success criterion whereby the lower limit of the 95% CI exceeded 20% for at least 2 of the 3 readers. The CLR was 85.6% (95% CI: 78.8%-92.3%) by Reader 1, 87.0% (95% CI: 80.4%-93.6%) by Reader 2, and 84.8% (95% CI: 77.8%-91.9%) by Reader 3. The true positive (TP) detection rate, defined as the percentage of patients who had a TP result confirmed by a truth standard out of all patients who underwent ^{18}F-DCFPyL PET/CT, was clinically meaningful, with TP detection rates of 42.8% (95% CI: 36.1%-49.5%) for Reader 1, 41.8% (95% CI: 35.1%-48.5%) for Reader 2, and 40.4% (95% CI: 33.7%-47.1%) for Reader 3. The primary endpoint was also analyzed based on ^{18}F-DCFPyL PET/CT local radiology interpretation. Local readers reported positive ^{18}F-DCFPyL scans in 69.2% (144/208) of patients. CLR was 80.3% (95% CI: 72.3% - 86.8%) and the TP detection rate was 49.0% (95% CI: 42.2% - 55.8%) for the local readers. The SOT was considered unevaluable for 11.5% to 15.9% of patients deemed to have positive ^{18}F-DCFPyL PET/CT scans by the three central readers.

More details of the nonclinical and clinical program, rationale for dose selection and data can be found in the IB for ^{18}F-DCFPyL Injection.

5.5. Study Rationale

In retrospective analyses, patients treated with enzalutamide following progression under abiraterone therapy of any duration, reported variable proportions of patients with >50% decline in PSA from baseline, ranging from 30–51%[21]. A study on mCRPC patients who received all available therapies at that time reported a ≥50% PSA response of 70.6% after 1st therapy[14].

The majority of data demonstrate limited benefit from enzalutamide in abiraterone-resistant patients. Resistance to abiraterone and subsequent response to enzalutamide may, for example, be caused by androgen receptor (AR) gain of function mutants enabling the AR to be activated by nonandrogenic steroids that do not require CYP17A1 for synthesis[22]. However, this is a rare event and response and resistance mechanisms are considered to be heterogenous and evolving with selective pressure of prescribed treatments. Cross-resistance might also involve tumor steroidogenesis as preclinical data support the role of tumor steroidogenesis as a mechanism of evolution to CRPC and resistance to enzalutamide[23]. Cross-resistance between docetaxel and abiraterone with lower than expected PSA response rate may exist in patients treated with docetaxel following abiraterone,[24] further narrowing treatment options for patients with mCRPC.

Furthermore, recent preclinical data suggest that the pro-apoptotic effects of enzalutamide could sensitize cells to radiotherapy induced cell death.[25] Thus, the combination of radiotherapy and enzalutamide could represent a potentially more effective treatment paradigm for patients with mCRPC.

The population failing mCRPC therapy with novel anti-androgens such as abiraterone are thus in need of effective alternative options and mechanism of action.

Specifically, I-131-1095 may prove beneficial in this treatment setting as it is unlikely to be affected by evolving anti-androgen or chemotherapy resistance with a tolerable safety profile. In summary, the combination of I-131-1095 with enzalutamide offers two potential additional advantages:

1. Antiandrogens such as enzalutamide have been shown to increase PSMA expression, the principle target of I-131-1095[26, 27]
2. Enzalutamide may enhance the lethality of radiation effects as evidenced in nonclinical studies[25, 28]

The present study consists of an open label randomized (2:1) trial of enzalutamide plus I-131-1095 or enzalutamide alone in taxane-naive patients with progressive mCRPC who have disease progression on abiraterone. The randomized study design was chosen to maximize the opportunity to provide objective information about the potential safety, tolerability and efficacy of I-131-1095 in a mCRPC post abiraterone clinical setting and to increase homogeneity and optimize potential benefit. To avoid unnecessary exposure of subjects to investigational therapy, all subjects will be assessed for PSMA expression by ^{18}F-DCFPyL PET/CT imaging (see Section 5.4) prior to randomization.

6. TRIAL OBJECTIVES AND PURPOSE

The objective of this study is to evaluate the safety and efficacy of I-131-1095, a novel PSMA-targeted radioligand therapy, in patients with progressive mCRPC who have disease progression on abiraterone and who are candidates for enzalutamide therapy.

6.1. Primary Objective

To determine the efficacy of I-131-1095 combined with enzalutamide compared to enzalutamide alone assessed by PSA response rate according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3)[29] criteria.

6.2. Secondary Objectives

Efficacy Objectives

- To determine the radiographic response of I-131-1095 combined with enzalutamide compared to enzalutamide alone based on PCWG3-modified RECIST 1.1 criteria[29,30]
- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on radiographic progression free survival (rPFS) as defined by RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on overall survival (OS)
- To evaluate the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on PSA kinetics
- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on duration of response
- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on time to initiation of any new treatment for prostate cancer

Safety Objectives

- To determine the safety and tolerability of I-131-1095 combined with enzalutamide

6.3. Exploratory Objectives

- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on PSMA-avid tumor burden using ^{18}F-DCFPyL PET/CT
- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on symptomatic skeletal events (SSEs)
- To evaluate patient reported quality of life outcomes
- To determine changes in automated bone scan index (aBSI) from baseline
- To determine changes in ECOG performance status from baseline

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a multicenter, open label, randomized phase 2 study of I-131-1095 radiotherapy (≤100 mCi/dose every 8 weeks for up to four doses) in combination with enzalutamide compared to enzalutamide alone in patients with progressive mCRPC. Patients must have documented progression on abiraterone and be indicated for treatment with enzalutamide. Patients must not have had prior treatment with taxane-based chemotherapy for CRPC and must be ineligible or refuse to receive chemotherapy at time of consent. Enzalutamide will be prescribed per approved labeling.

Approximately 120 subjects at approximately 30 sites in the United States and Canada will be centrally randomized in a 2:1 ratio (80 subjects to receive I-131-1095 plus enzalutamide versus 40 subjects to receive enzalutamide alone); randomization will be stratified by risk group (see Section 7.4). Subjects will undergo PSMA imaging with ^{18}F-DCFPyL PET/CT as part of Screening to confirm high PSMA expression, as evaluated by central review.

Safety data will be monitored during the Randomized Treatment Period on an ongoing basis by an independent Data Monitoring Committee (iDMC) and the Sponsor (see Section 7.8).

All subjects will be followed for one year following the first dose of Randomized treatment for the following assessments of prostate cancer: PSA, disease status on CT/MR, bone scan and ^{18}F-DCFPyL-PET, automated bone scan index, SSE, survival status, and patient reported outcomes (PROs). The consensus guidelines of the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) and the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria will be used by investigators to determine radiologic response and clinical and radiographic disease progression.[29,30]

Safety and tolerability will be assessed by the collection of treatment-emergent AEs, monitoring of vital signs and physical examinations, safety laboratory tests, and ECGs.

Subjects may discontinue early from the Randomized Treatment Period (see Section 8.3.2) but may choose to remain in the study to be followed for survival status.

Survival data, adverse events of special interest (AESIs; see Section 12.1.3) and new anti-cancer therapy will be collected via phone call visits for at least one year following completion or early discontinuation of the Randomized Treatment Period until the end of the study (whichever is later)

7.2. Trial Endpoints

7.2.1. Primary Endpoint

PSA response rate according to PCWG3[29] criteria defined as the first occurrence of a 50% or more decline in PSA from baseline, confirmed by a second measurement at least 3 weeks later.

7.2.2. Secondary Efficacy Endpoints

- Objective response rate (ORR) from Baseline to the final assessment performed for each patient defined as the proportion of patients who have a partial (PR) or complete response (CR) based on RECIST 1.1[30] for soft tissue or PCWG3[29] for bone (PCWG3-modified RECIST 1.1)

- rPFS defined as time from randomization to the first occurrence of radiographic progression based on RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
- OS defined as time from randomization to death from any cause
- PSA progression defined as the time from randomization to the date of the first PSA increase from Baseline ≥25% and ≥2ng/mL above nadir confirmed by a second PSA assessment defining progression ≥3 weeks later per PCWG3[29]
- Duration of response defined as the time from the first date of complete or partial response to the first occurrence of radiographic progression based on PCWG3-modified RECIST 1.1, or unequivocal clinical progression as defined in Section 11.1.3.2.
- Time to next treatment defined as the time from randomization to initiation of any new treatment of prostate cancer

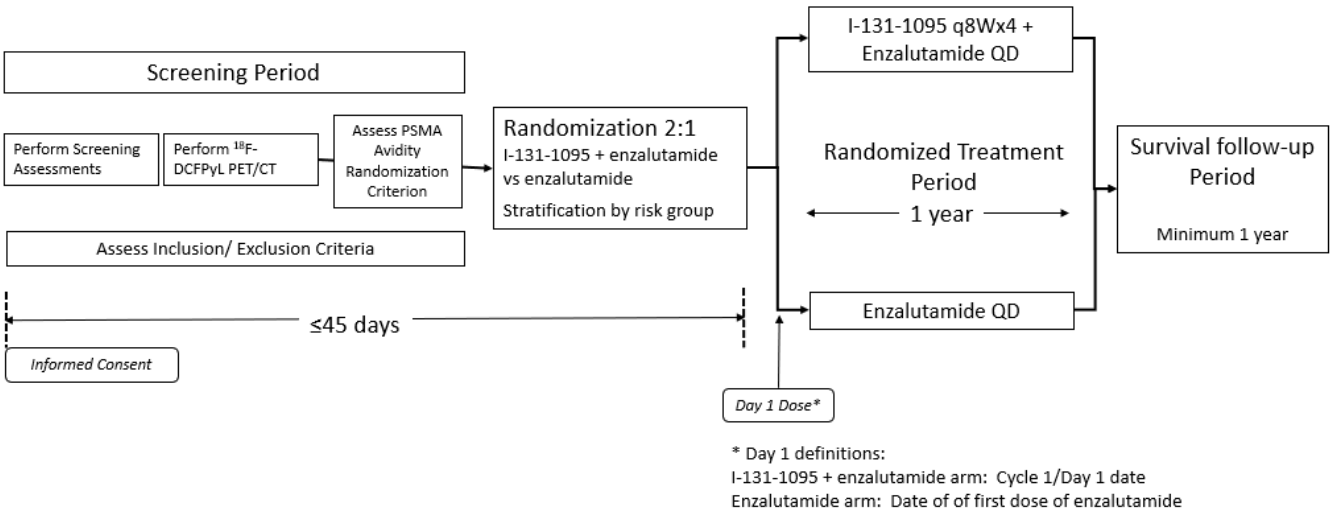
7.2.3. Exploratory Endpoints

- ^{18}F-DCFPyL uptake defined as change in SUV_{max} from baseline to each study defined timepoint
- ^{18}F-DCFPyL positive lesion counts defined as change from baseline to each study defined timepoint
- Time from randomization to first symptomatic skeletal event (SSE) defined as symptomatic fracture, radiation or surgery to the bone, or spinal cord compression
- The rate of pain progression, defined as an increase of ≥30% from baseline in the Brief Pain Inventory Short Form (BPI-SF)[31] pain intensity score at 6 months
- Overall and component scores of the "Functional Assessment of Cancer Therapy-Prostate (FACT-P)[32] questionnaire
- SF-12v2 domain scores, Physical Component Summary (PCS) scores and Mental Component Summary (MCS) scores
- Summary statistics for the EQ-5D-5L VAS
- Summary statistics for the EQ-5D-5L index
- aBSI scores
- ECOG performance status ratings

7.2.4. Safety Endpoints

- Incidences of treatment-emergent adverse events and SAEs by CTCAE v5.0
- Number of subjects discontinuing study drug due to adverse events
- Changes from baseline in physical exam findings, vital signs, clinical laboratory values, and ECG values
- Summaries of concomitant medication use

Figure 1: Study Schema



7.3. Number of Subjects

Approximately 175 subjects will be consented to randomize 120 subjects to either I-131-1095 plus enzalutamide or enzalutamide alone to meet the number of subjects required for assessment of the primary endpoint. See Section 8 for eligibility criteria and Section 13.1 for sample size assumptions.

7.4. Treatment Assignment

Subjects will be randomized to a treatment arm (I-131-1095 + enzalutamide vs. enzalutamide alone) based on the following stratification risk classes[33]:

- Intermediate risk PCa: Hgb ≥11 g/dL and LDH <262 IU/L and ALP<414 IU/L
- High-risk PCa: Hgb <11 g/dL or LDH ≥262 IU/L or ALP ≥ 414 IU/L

7.5. Study Duration

Subjects who provide informed consent will have screening procedures completed to assess eligibility criteria. Subjects expected to meet all eligibility criteria will receive ^{18}F-DCFPyL and PET/CT to assess the randomization criterion. If subjects do not demonstrate PSMA tumor avidity based on central assessment of avidity criteria defined in Section 8.4 their total study duration is estimated to be up to 45 days. Subject who meet all eligibility and randomization criteria will be randomized (2:1) to receive I-131-1095 plus enzalutamide or enzalutamide alone. Day 1 is defined as the date a patient receives the first dose of their randomized treatment. In the case of patients randomized to the I-131-1095 + enzalutamide arm, Day 1 will be the date they receive I-131-1095 as part of Cycle 1/Day 1. For patients randomized to the enzalutamide arm, their respective Day 1 is defined as the date they receive their first dose of enzalutamide. Patients who are scheduled to complete Day 1 > 30 days from when the Screening Hematology and/or Chemistry samples collected must have these laboratory assessments repeated to confirm that the patient still meets the associated entry criteria prior to receiving their first dose of randomized treatment. In addition, if a patient is scheduled to complete Day 1 > 45 days from

when a screening procedure is completed to determine eligibility, other than chemistry and hematology, the investigator should confirm that the patient still meets the criteria prior to receiving their first dose of randomized treatment. All patients will have scheduled follow-up visits in the Randomized Treatment Period for up to 12 months after their first dose of I-131-1095 and/or enzalutamide. The Randomized Treatment Period is comprised of approximately 20 visits, including up to four I-131-1095 dosing cycles (16 visits) with a dosimetry assessment prior to the third dosing cycle, and four additional safety/efficacy visits including an End of Treatment visit. A Dosing Cycle is defined as an 8-week period starting with Day 1 of randomized dosing. The start of a Dosing Cycle corresponds with the day of study drug administration for subjects receiving I-131-1095. A delay in dosing beyond the 8-week cycle is permitted up to an additional 6 weeks, or if a longer delay is necessary, as agreed upon with prior approval from the study Medical Monitor (see Section 7.7.1).

Subjects may discontinue early from the Randomized Treatment Period or from the study at any time as defined in Section 8.3 . Following early termination from or completion of the Randomized Treatment Period, patients are given the option to enter the Survival Follow-up Period during which survival data, adverse events of special interest (AESIs) and new anti-cancer therapy will be collected via phone call visits every 13 weeks for at least one year or to the end of the study (whichever is later) after the first dose of randomized treatment. As such, the maximum duration a patient may participate in the study is approximately 5 years. The end of study is defined as when the last patient completes the 1 year Survival Follow up visit (Week 105). Thus, the total maximum study duration for randomized subjects is approximately 5 years

7.6. Study Procedures

See Figure 1 for the Study Schema. All study procedures are summarized in the tabular form Table 3.

Table 3: Schedule of Assessments

All subjects, on-site visit All subjects, home visit option I-131-1095 arm only, home visit option	Screening Period		Randomized Treatment Period																				Survival follow-up[n] Period			
			Dosing Cycle 1				Dosing Cycle 2[w]				Dosimetry	Dosing Cycle 3[w]				Dosing Cycle 4[w]						EOT Visit[a]	Phone call visits every 13 weeks (+/- 7 days) until End of Study[v]			
Visit Week	-4 to -1		1[u]	3	5	7	9	11	13	15	13-14	17	19	21	23	25	27	29	31	36	42†	47†	53	66	79	92	105[v]
Study Day[b]	45 days		1[u]	15*†	29†	43	57	71*†	85†	99*†	85- 98	113	127*†	141†	155*†	169	183*†	197†	211*†	246	288	323	365	456	547	638	729[v]
Informed Consent	X																									
Eligibility Criteria	X	X[u]																								
Randomization[c]		X																								
Demographics	X																									
Medical/prostate cancer history and treatments	X																									
Physical Exam	X[u]						X[m]					X[m]				X[m]							X				
Vital Signs	X[s]		X[j]	X*	X	X	X[j]	X*	X	X*		X[j]	X*	X	X*	X[j]	X*	X	X*	X	X	X	X				
Weight	X	X	X			X	X				X	X				X				X			X				
12-lead ECG	X		X*[j/u]				X*[j]					X*[j]				X*[j]							X				
Chemistry, hematology	X		X[h]	X*	X	X	X[h]	X*	X	X*		X[h]	X*	X	X*	X[h]	X*	X	X*	X	X	X	X				
Urinalysis			X[h]				X[h]					X[h]				X[h]							X				
Testosterone	X																									
AR-V7	X																									
TSH, T4	X				X*		X*		X*			X*		X*		X*		X*		X*			X				
PSA (Total)[i]	X		X[h]		X		X[h, t]		X			X[h, t]		X		X[h, t]		X		X[t]	X	X	X				
Chest/abdomen/pelvis CT or MRI	X[r]						X[t]					X[t]				X[t]				X[t]			X				
Bone scan	X[r]						X[t]					X[t]				X[t]				X[t]			X				
^{18}F-DCFPyL administration		X[p]				X[p]																	X[p]				
^{18}F-DCFPyL PET/CT[o]		X[p]				X[p]																	X[p]				
Thyroid Blockage*[,d]			X*[,d]				X*[,d]				X*[,d]	X*[,d]				X*[,d]											
1095 administration			X*				X*[, e]				X (10 mCi)	X*[, e]				X*[, e]											
Dosimetry scans[f]											X*																
Enzalutamide SoC QD[g]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→				
Prior and Concomitant Medications	X	X[u]	X	X*	X	X	X	X*	X	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X	X	X	X[q]	X[q]	X[q]	X[q]
Adverse events		X[p/u]	X	X*	X	X	X	X*	X	X*	X*	X	X*	X	X*	X	X*	X	X*	X	X	X	X	X[l]	X[l]	X[l]	X[l]
ECOG	X																						X				
PROs[k]			X[h]				X[h, t]					X[h, t]				X[h, t]				X[t]			X				

BPI-SF = Brief Pain Inventory – Short Form; CRF = Case Report Form DLT = dose-limiting toxicity; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group performance status; EDC = Electronic Data Capture system; EOS = End of Study; EQ-5D-5L = EuroQol Group health-related quality of life assessment; FACT-P = Functional Assessment of Cancer Therapy – Prostate; SF-12 = 12-Item Short Form Health Survey version 2; SOC = Standard of Care

* Visits/procedures will only be done for subjects who received I-131-1095 dosing at the start of the current Dosing Cycle. TSH and T4 (free) will be collected during the entire Treatment Period at all indicated (*) visits regardless of having received additional Dosing Cycle(s).
† Visit may be completed by an appropriately delegated home health professional

a. End of Study (EOS) visit will be completed for all subjects who discontinue the study after beginning randomized treatment. If the following assessments were completed within 12 weeks of the EOS Visit, they do not need to be repeated: CT or MRI, Bone scan, ^{18}F-DCFPyL PET/CT.
b. Visit windows during Randomized Treatment Period are ± 5 days. Visit windows during the Survival follow-up period are ±7 days.
c. Randomization in EDC system after PyL read if PSMA avidity randomization criterion is met
d. The administration of potassium iodide should begin 24 hours prior to the administration of I-131-1095 and should continue for a total of 10 days.
e. Dosing during the 3rd and 4th cycles will depend on dosimetry results and recovery of any DLTs since the last administration of I-131-1095
f. Dosimetry will be performed prior to the planned 3rd therapeutic administration of I-131-1095. Following the injection of 10 mCi of I-131-1095, whole-body planar images and SPECT/CT scans of the chest and abdomen/pelvis will be acquired as follows:

	Hours after Dosing			
Dosimetry Schedule	0.5 - 4	18 - 30	42 -102	138 - 174
Planar Whole Body Scan	X (before voiding)	X (after voiding)	X (after voiding)	X (after voiding)
SPECT/CT (chest and abdomen/pelvis)		X (after whole body scan)		

g. Subject should self-administer oral enzalutamide as prescribed per approved labelling
h. Complete assessment pre-dose of I-131-1095, if receiving I-131-1095 dose. If the screening Hematology/Chemistry was performed > 30 days prior to Day 1, the pre-dose Hematology/Chemistry should be evaluated to confirm that the patient still meets study eligibility criteria prior to the administration of study drug.
i. If PSA lowers ≥50% from Day 1, PSA collection must be repeated at the next visit or unscheduled visit occurring at least 3 weeks later
j. Complete assessment both pre-dose and post-dose of I-131-1095 with the exception of Study Day 1 that requires a 12-lead ECG post-dose of I-131-1095 only.
k. The following health outcome assessments will be completed: BPI-SF, FACT-P, EQ-5D-5L, SF-12
l. Only adverse events of special interest (AESI) will be collected in the Survival Follow-up phase a (see “n” below)
m. Only brief physical exam will be conducted
n. During the Survival F/U Period, only secondary malignancies (including hematologic) and thyroid toxicities (hyper/hypothyroid) will be collected
o. ^{18}F-DCFPyL PET/CT scan is performed 60-120 minutes post ^{18}F-DCFPyL dosing from mid-thigh to skull vertex and prior to randomization. Additional unscheduled ^{18}F-DCFPyL PET/CT scan(s) may be performed with Sponsor approval.
p. Safety phone call follow up within 24-72 hours of ^{18}F-DCFPyL administration
q. Concomitant medications in the survival follow-up period include anti-cancer therapies only
r. If performed within 21 days of informed consent, does not need to be repeated during screening
s. Height will only be recorded at Screening
t. If subject’s dosing schedule is adjusted, efficacy assessments will remain at the scheduled timepoint
u. Day 1 is defined as the date of the first dose of I-131-1095 for subjects randomized to the I-131-1095 + Enzalutamide arm. For subjects randomized to the Enzalutamide Alone arm, Day 1 corresponds to the day the first enzalutamide dose is administered. If the screening Hematology/Chemistry was performed > 30 days prior to Day 1, the pre-dose Hematology/Chemistry should be evaluated to confirm that the patient still meets study eligibility criteria prior to the administration of study drug. If Day 1 is > 45 days from when a screening assessment (other than hematology or Chemistry as previously described) is performed to determine eligibility, the investigator should confirm that the patient still meets the relevant enrolment criteria
v. Patients will be followed as part of the Survival Follow-up Period every 13 weeks for a minimum of one year or until the overall end of study (whichever is greater)
w. If subject’s dosing schedule is adjusted, the subsequent dosing schedule and safety assessment schedule, e.g., Physical Exam, ECG, Vital Signs, and Safety will be updated to reflect the dosing adjustment, i.e., Subsequent doses will be scheduled at 8 week intervals and safety assessments will be conducted within the protocol specified timeframe in relation to the respective dose. In cases of dose schedule adjustments, efficacy assessments as identified in this table and Section 11.1 will remain at the scheduled timepoint as expected from the patient’s Day 1

7.6.1. Screening (Days -45 to Randomization)

Subject eligibility will be assessed and confirmed by the Investigator. All the inclusion criteria must be met and none of the exclusion criteria may apply. All Screening procedure results must be available before determining a subject's eligibility for the study. All protocol-specified procedures during Screening must occur within 45 days of Randomization. (except radiographic assessments as described below), otherwise the patient must be reconsented and Screening procedure(s) must be repeated.

The following procedures will be performed during Screening:

- Informed consent (see Section 16.3)
- Review of eligibility criteria
- Demographic information (see Section 10.1)
- Medical and prostate cancer history and treatments (see Section 10.2)
- Complete physical examination (see Section 11.2.2)
- Vital signs (blood pressure, heart rate, temperature, height and weight) (see Section 11.2.1)
- 12-lead ECG (see Section 11.2.3)
- Blood draw for laboratory assessments for analysis by the study assigned central laboratory (PSA, hematology, chemistry, testosterone, TSH, Free T4, and AR-V7; see Section 11.1.1 and Section 11.2.4)
- Imaging (unless performed within 21 days prior to consent; assessed locally and sent to Imaging Core Lab) (see Section 11.1.2):
  - Whole-body radionuclide bone scan
  - Chest/abdomen/pelvic CT/MRI
- ECOG performance status (see Section 11.1.6)
- Record prior medications taken within 30 days prior to Screening PyL dose (see Section 9.5)
- Plan to initiate enzalutamide therapy (see Section 9.3)

7.6.1.1. Additional Screening (Days -45 to Randomization)

Subjects who meet or are expected to meet all eligibility criteria during Screening will receive ^{18}F-DCFPyL dosing and whole-body PET/CT imaging (See Section 9.2.1.1.4 and Imaging Manual for additional details).

- Administer a prescribed dose of 9 mCi (333 MBq) ^{18}F-DCFPyL as defined in Section 9.2.1.1.4
- Within 60 – 120 minutes post-^{18}F-DCFPyL dosing, acquire a single PET/CT scan from mid-thigh to skull vertex

- Submit ^{18}F-DCFPyL PET/CT scan and baseline bone, CT and MR imaging studies to Central Imaging Core Lab for interpretation
- Record concomitant medications taken post-PyL dosing (see Section 9.5)

A Safety Phone Call will take place 24-72 hours after ^{18}F-DCFPyL dosing to collect any AEs or SAEs that occurred within 24 hours of ^{18}F-DCFPyL dosing (see Section 12 for complete details). The Central Imaging Core Lab will interpret the ^{18}F-DCFPyL PET/CT scan for PSMA avidity as defined in Section 8.4 to evaluate if the subject qualified for randomization. Then,

- Review of eligibility criteria to confirm whether the subject is eligible for the study

The following procedures should be performed for patients who qualify for randomization:

- Randomize eligible subject using Electronic Data Capture system (EDC). Subjects will be randomized to a treatment arm (I-131-1095 + enzalutamide vs. enzalutamide alone) based on stratification risk classes (see Section 7.4)

7.6.2. Randomized Treatment Period (Dosing Cycles 1-4; additional visits through Week 53)

The Randomized Treatment Period will begin with Day 1, corresponding to the first dose of I-131-1095 for subjects randomized to the I-131-1095 + Enzalutamide arm. For subjects randomized to the Enzalutamide Alone arm, Day 1 corresponds to the day the first enzalutamide dose is administered.

Patients who are scheduled to complete Day 1 > 30 days from when the Screening Hematology and/or Chemistry samples collected must have these laboratory assessments repeated to confirm that the patient still meets the associated entry criteria prior to receiving their first dose of randomized treatment. In addition, if a patient is scheduled to complete Day 1 > 45 days from when a screening procedure is completed to determine eligibility, other than chemistry and hematology, the investigator should confirm that the patient still meets the criteria prior to receiving their first dose of randomized treatment.

The Randomized Treatment Period is comprised of up to 20 visits including up to four Dosing Cycles (16 visits) with a dosimetry assessment (Section 7.6.2.6) prior to the third dosing cycle, followed by four additional safety/efficacy visits including an End of Study visit. A Dosing Cycle is defined as an 8-week interval starting with Day 1 with a total of 4 visits, each two weeks apart. During the Randomized Treatment Period some visits may or may not be performed depending on whether the subject received a dose of I-131-1095 during the Dosing Cycle, and some visits/ assessments may be conducted by an appropriately delegated home health care professional (see Table 3).

If subject's dosing schedule is adjusted, the subsequent dosing schedule and safety assessment schedule will be updated to reflect the dosing adjustment however, efficacy assessments as identified in Table 3 and Section 11.1 will remain at the scheduled timepoint as expected from the patient's Day 1.

7.6.2.1. First Day of each Dosing Cycle and/or Start of Weeks 1, 9, 17, and 25 and Week 36 (±5 days)

All subjects, regardless of randomized treatment arm, will have the following procedures performed at the start of Weeks 1, 9, 17, 25, and Week 36 as specified. For subjects receiving I-131-1095, all procedures below should be performed **before** I-131-1095 dosing. If subject's dosing schedule is adjusted, the subsequent dosing schedule and safety assessment schedule, e.g., Physical Exam, ECG, Vital Signs, and Safety will be updated to reflect the dosing adjustment, i.e., Subsequent doses will be scheduled at 8 week intervals (+/- 5 days) and safety assessments will be conducted within the protocol specified timeframe in relation to the respective dose. In cases of dose schedule adjustments, efficacy assessments as identified in Table 3 and Section 11.1 will remain at the scheduled timepoint as expected from the patient's Day 1

- Brief physical examination (see Section 11.2.2) at Weeks 9, 17 and 25
- Vital signs (blood pressure, heart rate, temperature); (see Section 11.2.1) at Weeks 1, 9, 17, 25, and 36
- Weight at Weeks 1, 9 ,17 and 25, and 36
- Blood draw for central laboratory assessments (PSA, hematology, chemistry; see Section 11.2.4 and 11.1.1) at Weeks 1, 9, 17, 25, and 36
  - For subjects dosed with I-131-1095, TSH and T4 (free) will be collected for central lab assessment at Weeks 9, 17, 25, and 36
  - For subjects receiving more than one dose of I-131-1095, a local assessment of hematological toxicity may also be completed prior to subsequent dosing (see Section 7.7)
- Urinalysis (see Table 8) at weeks 1, 9, 17, and 25
- Imaging (assessed locally and sent to Imaging Core Lab) at Weeks 9, 17, 25, and 36 only (see Section 11.1.2):
  - Whole-body radionuclide bone scan
  - Chest/abdomen/pelvic CT/MRI
- Review and record concomitant medications (see Section 9.5) at Weeks 1, 9, 17, 25, and 36
- Review and record adverse events (see Section 12.1) at Weeks 1, 9, 17, 25, and 36
- Patient Reported Outcomes (see Section 11.1.4) at Weeks 1, 9, 17, 25, and 36
- Review enzalutamide administration details with subject at Weeks 1, 9, 17, 25, and 36; Subjects may initiate enzalutamide treatment up to 7 days before Day 1 after Randomization. Record subject's enzalutamide dosing compliance at Weeks 9, 17, 25, and 36. (see Section 9.3)

Subjects Randomized to I-131-1095 Treatment Arm

For subjects receiving I-131-1095 during the Dosing Cycle, the additional procedures below should be performed:

At least 24 hours before administration of I-131-1095:

- Before administration of I-131-1095, the subject's thyroid must be blocked with inorganic iodine as prescribed per institution's standard of care to mitigate uptake of iodine-131 by the thyroid and reduce the risk of hypothyroidism following treatment with I-131-1095.
- The administration of potassium iodide for thyroid blockage should begin at least 24 hours prior to the administration of I-131-1095 and should continue for a total of 10 days. If thyroid blockade did not start at least 24 hours prior to initiation of I-131-1095, study drug administration must be delayed.

I-131-1095 study drug administration (First day of each dosing cycle)

- Administration of I-131-1095 must occur by the labeled expiration time. See Section 9.2.2.5 for administration details.
- To minimize irradiation of the urinary bladder, the subject should be encouraged to increase fluid intake (preferably at least 250 mL every 4-6 hours) and to void frequently through the first 2 days after administration. The subject's radioactive urine should also be handled and disposed of in a manner consistent with institutional and local policies.
- Applicable procedures and regulations for the management of patients receiving radioactive Iodine must be followed prior to subject release.
- Pre-dosing 12-lead ECG (see Section 11.2.3) on Day 1 of each dosing cycle that I-131-1095 therapeutic dosing occurs for the subject with exception the Dose 1
- The first dose of I-131-1095 will be 100 mCi. See Section 7.7 for subsequent dose adjustments due to dose limiting toxicities and Section 7.6.2.6 dosimetry assessment for eligibility of 3rd and 4th dose(s).

Post - I-131-1095 study drug administration (first day of each dosing cycle)

- Post-dosing vital signs (blood pressure, heart rate, temperature (see Section 11.2.1)
- Post-dosing 12-lead ECG (see Section 11.2.3) on Day 1 of each dosing cycle that I-131-1095 dosing occurs for the subject, including Dose 1 Record adverse events (see Section 12.1)
- Record any new concomitant medications or medical procedures received post-dosing (see Section 9.5)

7.6.2.2. I-131-1095 Safety Visits (2, 4, and 6 weeks after I-131-1095 dosing)

Subjects dosed with I-131-1095 during the current Dosing Cycle will have the following assessments performed 2, 4, and 6 weeks after I-131-1095 dosing (± 5 days) at a scheduled or

unscheduled visit. These assessments may be performed by an appropriately delegated home health care professional:

- Vital signs (blood pressure, heart rate, temperature); (see Section 11.2.1)
- Blood draw for central laboratory assessments (hematology, chemistry; see Section 11.2.4 and 11.1.1)
- Review and record concomitant medications (see Section 9.5)
- Review and record adverse events (see Section 12.1) and record subject's enzalutamide dosing compliance
- Review enzalutamide administration details with subject

7.6.2.3. Start of Weeks 5, 13, 21, 29, 42 and 47 (± 5 days)

For ALL subjects, the following assessments will be performed as indicated. This visit may be performed by an appropriately delegated home health care professional:

- Vital signs (blood pressure, heart rate, temperature); (see Section 11.2.1)
- Blood draw for central laboratory assessments (PSA, hematology, chemistry; see Section 11.2.4 and 11.1.1)
  - Subjects dosed with I-131-1095 will be tested for evidence of hypothyroidism by measuring levels of TSH, Free T4 at Weeks 5, 13, 21, and 29
- Review and record concomitant medications (see Section 9.5)
- Review and record adverse events (see Section 12.1)
- Review enzalutamide administration details with subject and record subject's enzalutamide dosing compliance

7.6.2.4. Week 7 Visit (± 5 days), All Subjects

All subjects, regardless of randomized treatment arm, will have the following procedures performed at Week 7; all procedures below should be performed before ^{18}F-DCFPyL dosing:

- Vital signs (blood pressure, heart rate, temperature); (see Section 11.2.1)
- Weight
- Blood draw for central laboratory assessments (hematology, chemistry; see Section 11.2.4 and 11.1.1)
- Review enzalutamide administration details with subject and record subject's enzalutamide dosing compliance
- ^{18}F-DCFPyL dosing and whole-body PET/CT scan (See Section 9.2.1.1.4 and Imaging Manual for additional details). All procedures above should be performed before ^{18}F-DCFPyL dosing
  - Administer a prescribed dose of 9 mCi (333 MBq) ^{18}F-DCFPyL as defined in Section 9.2.1.1.4

  - Within 60 – 120 minutes post-^{18}F-DCFPyL dosing, acquire a single PET/CT scan from mid-thigh to skull
  - Submit ^{18}F-DCFPyL PET/CT scan to Central Imaging Core Lab for interpretation
- Review and record concomitant medications (see Section 9.5)
- Review and record adverse events (see Section 12.1)
- A Safety Phone Call will take place 24-72 hours after ^{18}F-DCFPyL dosing to collect any AEs or SAEs that occurred within 24 hours of ^{18}F-DCFPyL dosing (see Section 12.1 for complete details)

7.6.2.5. Dosimetry (After the 2nd Therapeutic Dose and Prior to the 3rd Dosing Cycle/ Weeks 13-14), I-131-1095 Arm only

Only subjects planned to receive the third therapeutic dose of I-131-1095 will undergo the following procedures after the 2nd therapeutic dose. The central dosimetry assessment will calculate the radioactivity allowance for subsequent dose(s) as applicable. The I-131-1095 imaging dose for dosimetry must be administered no later than the start of Week 14 to allow for sufficient time for the central dosimetrist to complete all post-dose imaging, dosimetry calculations, and allow adjustments, as needed, to the Cycle 3 dose of I-131-1095 in time for the patient to receive their Cycle 3 I-131-1095 dose within the protocol specified timeframe.

At least 24 hours before receiving dosimetric dose (10 mCi) of I-131-1095:

- Before administration of I-131-1095 at 10 mCi, the subject's thyroid must be blocked with inorganic iodine (e.g., potassium iodide) as prescribed per institution's standard of care. Thyroid blockage should begin at least 24 hours prior to the administration of I-131-1095 and should continue for a total of 10 days after I-131-1095 administration. If thyroid blockade did not begin in time, study drug administration should be delayed.

I-131-1095 study drug administration (dosimetric dose):

- Administration of I-131-1095 must occur by the labeled expiration time. See Section 9.2.2.5 for administration details.
- To minimize irradiation of the urinary bladder, the subject should be encouraged to increase fluid intake (preferably at least 250 mL every 4-6 hours) and to void frequently through the first 2 days after administration. The subject's radioactive urine should also be handled and disposed of in a manner consistent with institutional and local policies.

Dosimetry Scans:

- An imaging standard will be prepared by adding approximately 0.5 mCi I-131-1095 to a saline infusion bag and imaged simultaneously with the subject using the same protocol. Consult the Site Imaging Manual for details about the standard preparation, camera set up and scanning procedures.
- The same gamma camera at a participating site must be used for all scans for a subject.

- Planar whole-body scans (anterior and posterior, from head to toe) will be performed at the below imaging time points below:
  - ***Image 1***: Within 0.5-4 hours post dosing and before subject voiding.
  - ***Image 2***: 18-30 hours post dosing and immediately after subject voiding.
  - ***Image 3***: 42-102 hours post dosing and immediately after subject voiding.
  - ***Image 4***: 138-174 hours post dosing and immediately after subject voiding.
- SPECT/CT of the chest and abdomen/pelvis (separate scans) will also be acquired at 18-30 hours post-dosing (after Image 2), to account for overlapping renal and bowel uptake[34]

All scans will be submitted to a Central Imaging Core Lab for processing and assessment. See Section 9.2.2.6 for additional Dosimetry information.

Upon completion of central dosimetry assessment, a calculated dosing regimen including the maximum cumulative dose and the total number of subsequent dose cycles (3rd and 4th dose(s), if any) each subject qualifies for will be communicated to the Investigator.

7.6.2.6. End of Treatment Visit – Start of Study Week 53 (±5 days) or When a Patient Prematurely Discontinues Randomized Treatment

The following procedures should be performed for ALL subjects. Subjects who discontinue the Randomized Treatment Period must return to the study site for an End of Treatment Visit.

- Complete physical examination (See Section 11.2.2)
- Vital signs (blood pressure, heart rate, temperature), height and weight (see Section 11.2.1)
- Laboratory assessments (PSA, hematology, chemistry, urinalysis, TSH, Free T4; See Section 11.1.1 and Section 11.2.4)
- 12-lead ECG (See Section 11.2.3)
- Imaging (assessed locally and sent to Imaging Core Lab) (see Section 11.1.2):
  - Whole-body radionuclide bone scan
  - Chest/abdomen/pelvic CT/MRI
- ECOG performance status (see Section 11.1.6)
- Patient Reported Outcomes (see Section 11.1.4)
- Review enzalutamide administration details with subject and record subject's enzalutamide dosing compliance
- ^{18}F-DCFPyL dosing and whole-body PET/CT scan (See Section 9.2.1.1.4 and Imaging Manual for additional details).
  - Administer a prescribed dose of 9 mCi (333 MBq) ^{18}F-DCFPyL as defined in Section 9.2.1.1.4

- Within 60 – 120 minutes post-^{18}F-DCFPyL dosing, acquire a single PET/CT scan from mid-thigh to skull
- Submit ^{18}F-DCFPyL PET/CT scan to Central Imaging Core Lab for interpretation
- A Safety Phone Call will take place 24-72 hours after ^{18}F-DCFPyL dosing to collect AEs or SAEs that occurred within 24 hours of ^{18}F-DCFPyL dosing; these will be recorded on the AE page of the eCRF and an SAE form if applicable.

- Review and record concomitant medications (see Section 9.5)
- Review and record adverse events (see Section 12.1)

7.6.3. Survival Follow-Up Period (Start of Study Weeks 66, 79, 92, 105 ± 7 days minimum, and every 13 weeks ± 7 days through the end of study)

Upon completion or early discontinuation of the Randomized Treatment Period subjects will enter the Survival Follow-Up Period. The following assessments will be collected every 13 weeks via a phone call, for at least one year after treatment completion or discontinuation, until the end of the study:

- Survival status. If the subject has died, date and cause of death should be obtained (see Section 11.1.5)
- Subsequent therapy for prostate cancer (see Section 13.2.2.3)
- Adverse events of special interest (see Section 12.1.3)

Reasonable effort should be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments and retrieve any outstanding data. Following 3 unsuccessful telephone contact attempts, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Alternate contacts should be attempted if the subject cannot be reached (e.g., primary care providers, referring physician, etc.). If after 30 days from the time that the site last had contact with the subject, 3 telephone attempts and one mail attempt was made, and the subject still cannot be reached the site must document that the subject is lost to follow up in the database and such efforts should be documented in the source documents.

7.6.4. Unscheduled Visit(s)

Unscheduled visits may be performed by site staff or an appropriately delegated home health care professional at any time during the study whenever necessary to assess for or follow-up on AEs, at the subject's request, or as deemed necessary by the Investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities may be completed at Unscheduled visits:

- Physical examination, as applicable
- Vital signs (blood pressure, heart rate, temperature, height and weight), as applicable
- ^{18}F-DCFPyL PET/CT scan(s) may be performed with Sponsor approval
- 12-lead ECG (if medically indicated)

- Laboratory assessments (PSA, hematology, chemistry, TSH, free T4, Urinalysis), as applicable
- Assessment of concomitant medications and medical procedures
- Assessment adverse events

7.7. Dose Adjustment Criteria

7.7.1. I-131-1095 Dose Limiting Toxicity and Dose Adjustment

If a subject experience any of the following dose limiting toxicities, subsequent I-131-1095 dose(s) should be prescribed at 75 mCi (2.775 GBq):

- CTCAE v5.0 ≥ Grade 3 neutropenia with fever consisting of ANC <1.0 x10^9/L with a single temperature measurement of >38.3°C (101ºF) or sustained temperature of ≥38°C (100.4°F) for more than one hour.
- CTCAE v5.0 Grade 3 thrombocytopenia (platelet count <50.0 x10^9/L – 25.0 x10^9/L) with bleeding (WHO bleeding scale) ≥ Grade 2 bleeding or CTCAE v5.0 Grade 4 thrombocytopenia (platelet count <25.0 x10^9/L) lasting 1 week with or without bleeding or platelet count < 10,000/µL at any timepoint.
- CTCAE v5.0 ≥ Grade 3 non-hematologic AEs (with the exception of any of the following: lab abnormalities [including INR, AST/ALT, AP] that improve to ≤ Grade 2 within 2 weeks, or pain, constipation, fatigue, decreased appetite, dehydration, dizziness, headache, dysgeusia, weight loss, xerostomia, sialadenitis, stomatitis, mucositis, alopecia, nausea, vomiting, and diarrhea, or when the AE can be positively attributed to a cause other than study drug).
- Other clinically significant drug-related toxicities deemed by the Investigator to be dose limiting or that causes the subject to withdraw from the study

Subjects should not receive any subsequent doses of I-131-1095 unless hematologic values return to baseline or levels no greater than CTCAE v5.0 Grade 1. The administration of the subsequent dose may be delayed for up to 14 weeks following the previous dose to allow for adequate hematologic recovery. If hematologic recovery to baseline or values no greater than CTCAE v5.0 Grade 1 has not occurred within 14 weeks following the previous dose, the subject will not receive further dosing with I-131-1095 unless prior approval is granted by the study Medical Monitor.

The administration of the subsequent dose may also be delayed for up to 14 weeks following previous dose due to other medical conditions or logistical reasons. Additional delay beyond this timeframe may be permitted with prior approval by the study Medical Monitor.

If prior approval is not granted, the subject will be asked to remain in the study to follow disease progression, safety and survival status.

7.8. Independent Data Monitoring Committee (iDMC)

An independent Data Monitoring Committee (iDMC) will be established for this study to safeguard integrity of the study and the interests of the trial participants, potential participants,

investigators, and Sponsor. Furthermore, the iDMC will assess the safety and efficacy of the trial's interventions, and to monitor the trial's overall conduct, and protect its validity and credibility. The iDMC will also review the results of the interim analysis for efficacy (see Section 13.2.4). The detailed procedures and composition of members is described in the Data Monitoring Committee Charter.

At the beginning of the study, the iDMC will assess emergent dose-limiting toxicities (DLTs) for individual subjects up to the first six subjects treated with I-131-1095. If DLTs are observed in more than 1 subject, the iDMC may propose changes to the dose or dose regimen (see Section 7.7). The iDMC will continue to meet regularly to assess subject safety throughout the Randomized Treatment period, as defined in the iDMC Charter.

7.9. Criteria for Study Termination

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

- If any significant safety issues occur;
- Failure of the Investigator to comply with pertinent ICH E6 guidelines on Good Clinical Practice (GCP) guidelines and regulations;
- If significant protocol violations occur;
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or other party involved in the study;

Failure of the Investigator to enroll subjects into the study at an acceptable rate as agreed-upon with the Sponsor.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for this study:

1. Male ≥ 18 years of age
2. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features at initial diagnosis
3. Castration-resistant prostate cancer, with serum testosterone ≤ 50 ng/dL (1.73 nM) at Screening
4. Metastatic disease documented by bone lesions on whole body bone scan or soft tissue lesions measurable per RECIST 1.1 on CT/MRI prior to Randomization or up to 21 days prior to Screening
5. Evidence of disease progression on prior abiraterone therapy. Disease progression is defined by meeting at least one of the following criteria:
   a. PSA progression as defined by a minimum of two rising PSA levels at least 1 week apart
      **Distinct from PCWG3 criteria which is used for the determination of PSA progression for study purposes following randomization*
   b. Soft tissue disease progression* defined by RECIST 1.1
   c. Bone disease progression* defined by two or more new lesions on bone scan

   **For subjects enrolling on the basis of soft tissue or bone progression, the baseline scan must show progression relative to a comparison scan performed during prior abiraterone therapy or after discontinuation from abiraterone. If the comparison scan is not available, the baseline scan report must reference the previous scan to document progression*
6. Planned to receive treatment with enzalutamide
7. Subjects who are ineligible or choose not to receive taxane-based chemotherapy based on personal preference or physician opinion. Examples of conditions that could make a patient ineligible or refuse to receive taxane-based chemotherapy, but would allow them to still be eligible to receive I-131-1095 include the following:
   a. Poor performance status
   b. Prior intolerance to cytotoxic agents
   c. History of another malignancy suspected for recurrence or metastases
   d. Other serious medical conditions such as symptomatic peripheral neuropathy CTCAE Grade 2 or higher; or clinically significant cardiovascular disease per the Investigator or treating physician
8. Subjects receiving bisphosphonate therapy must have been on stable doses for ≥ 4 weeks prior to Randomization
9. Eastern Cooperative Oncology Group (ECOG) performance status 0-2

10. If sexually active, agree to use a medically acceptable method of birth control (e.g., spermicide in conjunction with a barrier such as a condom) or sexual abstinence from the time of dosing through 28 days after the last dose of I-131-1095. Sperm donation is prohibited from the time of dosing through 28 days after the last dose of I-131-1095. Female partners must use hormonal or barrier contraception unless postmenopausal or abstinent.
11. Estimated life expectancy of at least 6 months as determined by the Investigator or treating physician.
12. Able and willing to provide signed informed consent and comply with protocol requirements

8.2. Subject Exclusion Criteria

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

1. Received any anti-tumor therapy within 4 weeks of Randomization, with the exception of abiraterone, GnRH therapy and non-radioactive bone-targeted agents
2. Received prior chemotherapy for castration-resistant prostate cancer

   ** Prior taxane based chemotherapy in a hormonal setting is allowed*
3. Superscan as evidenced on baseline bone scan (defined as extensive significant uptake demonstrated throughout the axial, proximal and peripheral skeleton system)
4. Treatment with Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223 within 6 months prior to Randomization
5. Prior hemi-body irradiation
6. Prior PSMA-targeted radioligand therapy
7. Major surgery within 4 weeks of Randomization
8. Impaired organ function as evidenced by the following laboratory values in Screening labs:
   a. Absolute neutrophil count < 1500 µL
   b. Platelet count < 100,000/µL
   c. Hemoglobin < 9.5 g/dL
   d. Albumin < 3.0 g/dL (30 g/L)
   e. Total bilirubin > 2 x ULN unless in instances of known or suspected Gilbert's disease
   f. AST or ALT > 2.5 x ULN
   g. Calculated creatinine clearance (CrCL) < 30 mL/min (Cockroft-Gault equation), or currently on renal dialysis.
9. QT interval corrected for heart rate (QTc) >470 msec during Screening
10. Previous use of enzalutamide for >7 days prior to consent
11. Planned initiation of alternative therapy for prostate cancer, investigational therapy, or participation in clinical trials during the study

12. History or risk of seizure (i.e., clinically significant neurological disorder) or any other condition that contraindicates treatment with enzalutamide (Xtandi®) as per the package insert
13. Gastrointestinal disorder affecting absorption of oral medications
14. Known or suspected brain metastasis or active leptomeningeal disease
15. Active malignancy other than prostate cancer, with the exception of curatively treated non-melanoma skin cancer, carcinoma in situ, or non-muscle invasive bladder/urothelial cancer
16. Active urinary incontinence
17. Subjects with any medical condition or other circumstances that, in the opinion of the investigator, compromise obtaining reliable data, achieving study objectives, or completing the study.

8.3. Subject Withdrawal Criteria

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

- Significant protocol violation or noncompliance
- Adverse event that precludes further study participation
- Investigator decision (e.g. change in therapy)
- Sponsor terminates the study
- Subject requests to be withdrawn from the study
- Subject is lost to follow-up
- Death

If a subject withdraws from study drug dosing or the Investigator withdraws the subject from receiving study drug, the subject should remain in the study to be followed for radiographic assessments in the absence of disease progression and having started another anti-cancer therapy, or at minimum for survival status and subsequent anti-cancer therapies.

Should a subject withdraw consent from the study, all efforts will be made to complete the required study procedures as thoroughly as possible prior to withdrawal. Data will be collected for all subjects up until the time consent is withdrawn. The reason for discontinuation will be recorded in the eCRF.

Subjects that terminate after being randomized will not be replaced.

8.3.1. Withdrawal of Subjects from Therapy due to Adverse Events

Any adverse event (AE) that is intolerable to the subject and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the Investigator or Medical Monitor would lead to undue risk to the subject if therapy continued. If a subject withdraws from

therapy due to an adverse event, he should continue to be followed up for efficacy in the Randomized Treatment Period up to Week 53 or until it is determined that their mCRPC has progressed.

8.3.2. Maintenance of Therapy in the Setting of Disease Progression

Randomized Treatment should be continued as long as the subject is benefiting from and tolerating the therapy. If a subject is deemed to be no longer benefiting from study therapy and one of the following events occur, study therapy should be discontinued: 1) unequivocal clinical progression (see Section 11.1.3.2), 2) radiographic disease progression (see Section 11.1.3.1), or 3) death.

Discontinuation of study drug due to PSA rise alone without evidence of confirmed radiographic or unequivocal clinical progression is discouraged.

8.4. Randomization Criterion

Subjects must also be screened for ^{18}F-DCFPyL avidity as defined by the below criteria to proceed to Randomization:

- ^{18}F-DCFPyL PET/CT imaging shows significant PSMA uptake (SUV_{max} > 1x liver SUV_{mean}) in all prostate cancer lesions, except as noted below:
    - PSMA negative soft tissue lesions < 1.0 cm in short axis;
    - PSMA negative lymph node lesions < 1.5 cm in short axis;
    - PSMA negative bone lesions with a soft tissue component < 1.0 cm in short axis or without a soft tissue component of any size

9. TREATMENT OF SUBJECTS

All subjects will self-administer enzalutamide as prescribed based on approved Prescribing Information (see Section 9.2). Subjects may initiate enzalutamide up to 7 days before Day 1.

9.1. Study Drug Regimen

This is an open-label study. All subjects will receive a dose of ^{18}F-DCFPyL Injection prior to randomization to assess PSMA avidity.

Following screening and PyL imaging, subjects will be centrally randomized in a 2:1 ratio (80 subjects in the I-131-1095 arm and 40 subjects in the control arm); randomization will be stratified by risk group according to Section 7.4.

9.1.1. Method of Assigning Subjects to Treatment Groups and Subject ID Number

Subject ID numbers will be comprised of a 3-digit site number followed by a 3 digit-patient number sequentially assigned as patients consent to the study. The EDC system will randomize eligible subjects and assign treatment groups (see Section 7.4).

9.2. Investigational Products (IP)

9.2.1. ^{18}F-DCFPyL

9.2.1.1. Description of ^{18}F-DCFPyL

A single administration of ^{18}F-DCFPyL Injection (PyL) will be administered prior to PET/CT imaging at the Enrollment Visit. See Table 4 for ^{18}F-DCFPyL Injection Drug Product characteristics. Additional information is provided in the IB and Imaging Manual.

Table 4: ^{18}F-DCFPyL Drug Product Characteristics

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

9.2.1.1.1. ^{18}F-DCFPyL Packaging and Labeling

The final drug product (PyL) is a clear, particulate-free injectable solution at a strength of 1-90 mCi/mL (37-3330 MBq/mL) at End of Synthesis (EOS). ^{18}F-DCFPyL will be dispensed and filled into a unit-dose syringe. The final drug product will be placed into a lead shield unit-dose system and delivered to the clinical site.

If there are any discrepancies (e.g. the description on the unit-dose label or quantity of unit-doses doesn't match the packing slip, the shipping box is visibly damaged), do not use the product and contact the reference noted on the Acknowledgement of Receipt.

Labels will be generated according to local and federal policies and meet minimum requirements for labeling radioactive materials in compliance with federal, state, and local pharmacy regulations. Progenics minimum requirements for the syringe label will include the following: subject identifier, product name, dispensing lot number, ordered dose, dispense date/time, dispensed activity and volume, and beyond use date. "New Drug—Limited by Federal Law to Investigational Use" will be included on the prescription label of the lead shield unit-dose system for each unit-dose syringe and the radioactive hazard symbol.

9.2.1.1.2. ^{18}F-DCFPyL Storage

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

9.2.1.1.3. ^{18}F-DCFPyL Handling, Preparation, and Disposal

Institutional policies and procedures should be followed for receipt, appropriate radiation safety handling and disposal. The final drug product is supplied to each institution on the day of administration in a unit-dose syringe (contained in the lead shield unit-dose system) with no additional preparation required.

9.2.1.1.4. ^{18}F-DCFPyL Administration

Administration of ^{18}F-DCFPyL Injection must occur by the labeled expiration time. Verify the clock used to record time of measurements and injection is correct and is synchronized with the clocks on the PET scanner and dose calibrator. Before and after each administration, measure the amount of radioactivity in the syringe in the dose calibrator. Record the exact times of dose calibration and time of injection. The decay-corrected administered dose will be calculated in the electronic database management system when the dose measurements and times are entered in the eCRF. Please see the Imaging Manual for complete details including pre and post-injection measurement of the ^{18}F-DCFPyL Injection dose syringe.

Please see the Imaging Manual for complete details including pre- and post-injection measurement of the ^{18}F-DCFPyL Injection dose syringe.

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

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

- Try to aspirate as much extravasated drug as possible through the still-intact catheter. Any of the dose remaining should be measured and recorded to permit correction of the administered dose for radioactive decay.
- Imaging should proceed unless contraindicated for safety reasons.

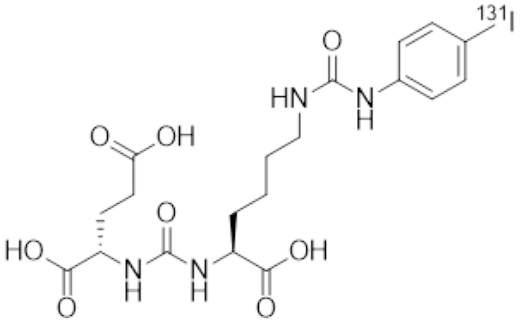
- Notify the responsible physician of the extravasation (location and estimated amount).
- Examine the skin area for local toxicity before discharge; instruct subject to contact site immediately or go to local Emergency Department if local symptoms at injection site do not improve or worsen.
- Note the extravasation as an Adverse Event in the eCRF.

9.2.2. I-131-1095

9.2.2.1. Description of I-131-1095

I-131-1095 for the PSMA-targeted treatment of prostate cancer will be administered following randomization. See Table 5 for I-131-1095 Drug Product characteristics. Additional information is provided in the IB and I-131-1095 Pharmacy and Dose Administration Manual.

Table 5: I-131-1095 Drug Product Characteristics

	Investigational Drug Product Characteristics
Product Name	I-131-1095 Injection
Pharmacological Class	Radiolabeled small molecule that is a highly selective prostate specific membrane antigen (PSMA) inhibitor
Chemical Name	((S)-2-(3-((S)-1-carboxy-5-(3-(4-[(131)I]iodophenyl)ureido)pentyl)ureido)pentanedioic acid
Formula	[I-131]-C19H25IN4O8
Chemical Structure	
Molecular Weight	568.33 g/mol
Radioactive Concentration	15.0-18.5 mCi/mL (0.555 to 0.685 GBq/mL) at Time of Calibration (TOC) in each vial
Dosage Form	Sterile solution for intravenous (IV) administration
Unit Dose	30-mL vial with 2 or 12-mL fill
Route of Administration	Dosimetric dose: Intravenous injection. Therapeutic dose: Intravenous infusion
Appearance and Color	Clear solution, colorless to yellow, free of visible particles

9.2.2.2. I-131-1095 Packaging and Labeling

I-131-1095 is supplied in a 30mL Type 1 glass vial that is capped with a gray septum and aluminum crimp. Excipients include ascorbic acid and gentisic acid at pH 4.5-5.5. The amount of unbound I-131 in each vial is ≤ 3.5%.

I-131-1095 is stored frozen in a lead shield to limit exposure and shipped on dry ice in an International Air Transportation approved package. The package is marked with the appropriate radioactive label. Upon receipt, the IP should be removed from the dry ice and stored in a freezer at ≤ -70°C in the lead pot or thawed for immediate use.

If there are any discrepancies (e.g. the description on the lead pot label or quantity of vials doesn't match the packing slip, the shipping box is visibly damaged or is devoid of dry ice upon delivery), do not use the product and contact the reference noted on the Acknowledgement of Receipt.

Labels will be generated according to local and federal policies and meet minimum requirements for labeling radioactive materials in compliance with federal, state, and local pharmacy regulations. Progenics minimum requirements for the prescribing label include but are not limited to: Subject identifier, product name, lot number, prescribed dose, volume, dispense date, expiration date, "For Investigational Use Only," and the radioactive hazard symbol.

Please see I-131-1095 Pharmacy and Dose Administration Manual for detailed information.

9.2.2.3. I-131-1095 Storage

The drug must be stored frozen in a lead pot at ≤ -70°C at the clinical site. The shelf life is 15 days post day of manufacture and 13 days post the Time of Calibration (ToC) when stored at ≤ -70°C; discard appropriately at 312 hours (13 days) post ToC.

9.2.2.4. I-131-1095 Handling, Preparation, and Disposal

The IP should be thawed in a room temperature setting in the lead pot prior to administration. Once the IP has been thawed, it cannot be refrozen and will remain stable when diluted with 0.9% Sodium Chloride and stored in its original packaging. The diluted solution should be administered to the subject within 8 hours after removal from ≤ -70°C storage.

I-131-1095 is radioactive and should only be handled by personnel trained and experienced in the use and disposal of radiopharmaceuticals according to institutional protocols and applicable state and federal regulations. Protective equipment, aseptic procedures and proper monitoring should be used and followed during dose administration. Unused or residual investigational product and the supplies used to prepare doses should be disposed of as radioactive waste following the institution's SOP and/or applicable regulations or guidances.

9.2.2.5. I-131-1095 Administration

Administration of I-131-1095 must occur by the labeled expiration time. The time of all measurements should be documented in reference to a single clock. If possible, the clock on the dose calibrator should be synchronized to this reference clock. Before and after each administration, measure the amount of radioactivity in the vial or syringe (depending on infusion method performed) and intravenous tubing in the dose calibrator. Record the exact times of dose

calibration and time of injection. The decay-corrected administered dose will be calculated in the electronic database management system when the dose measurements and times are entered in the eCRF.

- **At least 24 hours before administering a dosimetric dose (10 mCi) of I-131-1095:** Before administration of I-131-1095 at 10 mCi, the subject's thyroid must be blocked with inorganic iodine (e.g., potassium iodide) as prescribed per institution's standard of care. Thyroid blockage should begin at least 24 hours prior to the administration of I-131-1095 and should continue for a total of 10 days after I-131-1095 administration. If thyroid blockade did not begin in time, study drug administration should be delayed.
- Before I-131-1095 injection, an indwelling intravenous (IV) catheter will be inserted into the antecubital vein (or an equivalent vein) of one arm, and then connected to an intravenous drip of normal saline.
- **Dosimetric Dose**: I-131-1095 is to be diluted with saline to achieve radioactivity concentration of approximately 2 mCi/mL. A volume of a diluted preparation corresponding to 10 mCi dose will be administered by a slow bolus injection, and the IV line will be flushed with at least 10 mL of saline to ensure full delivery of the dose
- **Therapeutic Dose**: I-131-1095 is to be diluted with saline up to a total volume of approximately 30 mL and the dose should be administered slowly with careful observation to be sure the dose is not extravasated. The suggested rate of infusion is approximately 60 mL/hr The IV line will be flushed with at least 10 mL of saline to ensure full delivery of the dose.
- An interruption in an infusion will be allowed to accommodate subject issues (e.g., toilet, nausea, vomiting, anxiety, etc). Most of these are avoidable by good subject education and IP administration planning. The subject's infusion should not be discontinued unless the Investigator determines that continuing would represent an unacceptable risk, undue safety hazard, or if subject's medical condition deteriorates rapidly and the infusion cannot continue or would interfere with medical or surgical care. If the infusion is expected to finish on the day scheduled, it may proceed even with interruptions.
- Any issues with the infusion (e.g., overdose, observable extravasation) will be recorded in the subject's record and transcribed onto the AE page of the case report form (CRF). The dose administered should be within 20% of the prescribed dose.

Please see I-131-1095 Pharmacy and Dose Administration Manual for detailed information.

9.2.2.6. I-131-1095 Dosimetry Assessment for Individual Subjects

The dosimetry evaluation will be conducted after the 2nd therapeutic dose and prior to the planned third therapeutic dose of I-131-1095 to determine the maximum cumulative dose and the total number of subsequent dose cycles each subject qualifies for (0-2) based on the absorbed radiation exposure limits to the subject's critical organs. Following administration of 10 mCi of I-131-1095, planar whole-body images and SPECT/CT of both the chest and abdomen/pelvis will be acquired at timepoints indicated in Section 7.6.2.5.

A central imaging lab will receive images in order to prepare them for a nuclear physicist who will perform dosimetry calculations. Regions/Volumes of interest (ROIs/VOIs) will be created

on a standard set of normal organs and/or other tissues that show significant uptake using CT as a guide; normal tissues will include at least salivary glands, brain, myocardium, kidneys, liver, lungs, spleen and thyroid for the purposes of determining activity and/or background subtraction factors. ROIs/VOIs will be copied to all dosing time points and adjusted as required by repositioning of the subject. The resultant ROI/VOI statistics will be used to quantify the activity in the organs as per established methodologies as clinically feasible and appropriate.[35,36,37,38] Whole body clearance will be used to estimate dose to the urinary bladder, using the OLINDA/EXM v2 dynamic bladder model.[39] For soft tissue tumors, if performed, doses will be estimated using the 'unit density sphere' model in OLINDA/EXM v2.

Time activity curves for organs will be modeled using exponential curves using OLINDA/EXM v2 software and radiation dose calculations will be made after adjusting the standard set of organ volumes used by OLINDA/EXM 2 to the critical organ volumes (to include at least kidneys) of the subject as measured by CT when available.

Based on individual dosimetry results, the maximum administered activity associated with absorbed radiation dose for specific critical organs, kidneys, liver, lungs, or bone marrow not exceeding the equivalent normal tissue tolerance to external beam radiotherapy of 18, 30, 18 and 10 Gy, respectively, based on ICRP Publication 118[16] will be calculated. The number of subsequent cycles of either 75 mCi or 100 mCi per treatment cycle will be approved by the study sponsor prior the assignment of subsequent doses, subject to recovery of any dose limiting toxicities (see Section 7.7)

9.3. Enzalutamide

All subjects will self-administer enzalutamide as prescribed by the investigator based on approved Prescribing Information.

Subjects may initiate enzalutamide after Randomization, up to 7 days before Day 1.

Enzalutamide is an approved drug that is commonly used as standard of care therapy for prostate cancer and is required to be used by all patients randomized in the study.

9.4. Blinding

This is an open label study.

9.5. Prior and Concomitant Therapy

All prior medications and medical procedures taken/occurring within 30 days before PyL dosing will be recorded in the eCRF. Concomitant medications are those taken from day of PyL dosing through the Randomized Treatment Period (End of Treatment visit). Any new therapies for prostate cancer will also be collected through the Survival Follow-up Period. Any new or changed concomitant medication(s) and medical procedures from the previous study visit must be recorded in the eCRF.

Prior and concomitant medications include all systemic therapies (single agent or in combination), including all prostate cancer related therapies administered, will be collected. Indications for each prior and concomitant medication will be recorded in the eCRF. Start and stop dates or duration, dose schedule of agents and indication will be captured. Vitamins, herbal

remedies, over the counter, and prescription medications will also be captured. If an intermittent or as needed (prn) use of any medication during the study is due to an adverse event (AE), then the AE must also be recorded on the AE page of the eCRF.

Subjects may initiate enzalutamide up to 7 days before Day 1.

9.5.1. Prohibited Medications

Enzalutamide use during the Screening Period is prohibited. Subjects may initiate enzalutamide treatment after Randomization up to 7 days before Day 1.

The following medications are prohibited during participation in the study, unless otherwise indicated below:

- Any contraindications for Enzalutamide/Xtandi® as per approved Prescribing Information.
- Subjects who receive concomitant investigational or new anticancer therapy for prostate cancer not listed below as permitted anytime during the study will be discontinued from the study.

9.5.2. Permitted Medications

Doses of the following medication classes should be maintained during the Screening Phase and while actively treated with study drug during the Treatment Period:

- Bisphosphonates or other approved bone targeting agents for the treatment of metastatic prostate cancer. Treatment interval is per the treating physician's discretion.
- Gonadotropin-releasing hormone (GnRH) analogues
- Anti-androgen therapy must be continued during the trial. If anti-androgen therapy is discontinued, the patient must be withdrawn from study treatment.

The following treatments are allowed during the study (and do not require study drug discontinuation) including, but not limited to:

- Blood transfusions and growth factor support per standard of care and institutional guidelines;
- Steroids given for the purpose of prevention and treatment of infusion/transfusion reactions or asthma or edema (e.g., equivalent daily dose of 10 mg of prednisone) Steroids used for immunomodulating purposes for the cancer is not permitted;
- Pain therapy per standard of care and institutional guidelines;
- Palliative radiation therapy including external beam radiotherapy (EBRT);
- Palliative surgical procedures to treat skeletal-related events and symptomatic skeletal events.

All medications and procedures are to be recorded on the concomitant medication case report form.

9.6. Treatment Compliance

^{18}F-DCFPyL and I-131-1095 will be administered under the supervision of the investigator or qualified designee. Details of the study drug injection will be captured in each subject's source documents.

Enzalutamide is self-administered orally once daily. Subjects will be instructed to take enzalutamide at approximately the same time each day as prescribed according to approved drug labeling. If dosing is missed on one day for any reason, double-dosing should NOT occur the following day but the prescribed dose should be resumed instead. Subjects will be asked at each study visit about their adherence in taking enzalutamide. Subjects will be asked to track their use of enzalutamide in a patient diary.

9.6.1. Drug Accountability

In accordance with ICH and US FDA requirements, the Investigator and/or drug dispenser must at all times account for all IP/study drug furnished to the institution and prepared for the subject. Accurate and adequate accountability records must be maintained by the study team for receipt and dispensation of study drug in an appropriate Drug Accountability record. Records should include at minimum:

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

All IP must be accounted for, whether used or unused, during the course of and at the conclusion of the study. The investigator is responsible for ensuring that study drug is administered only to subjects included in this study in accordance with the study protocol.

The shipment of drugs from the Sponsor to the Investigator or other designated persons cooperating with the Investigator will be accompanied by a receipt form that indicates the lot number(s) and the amount of drug provided for the study. The Investigator is responsible for ensuring that deliveries of study drugs are correctly received and recorded and handled and stored safely and properly in accordance with the Code of Federal Regulations (CFR), local/state laws and used in accordance with this protocol. Unused product will be disposed of according to institutional regulations. Record the use and/or disposal of the study drug in the drug accountability logs. Throughout the study, drug accountability will be performed by appropriate Sponsor representative(s) and when appropriate, reconciliation will be performed.

10. ASSESSMENT OF BASELINE

10.1. Demographics and Medical History

Demographic and baseline information, including date of birth (DOB), race, ethnicity, prostate cancer (e.g. diagnosis and staging information) and medical history, testosterone and AR-V7 status will be collected and recorded in the eCRF to describe the study population.

Medical history will include prostate disease history, prostate cancer staging, biopsy results, and all past/present cancer-related therapies. Other clinically relevant medical history, including chronic conditions whether or not corresponding medications are taken for the condition, will be recorded prior to study drug administration. This should include any past and/or current medical conditions that, in the opinion of the investigator, are clinically relevant regardless of whether it has resolved. All conditions that correspond with the subject's medications will be recorded in the eCRF. Historical information concerning allergies (classification as food, drug and/or environmental) will also be obtained.

10.2. Prior Prostate Cancer Systemic Therapies

All prior systemic therapies (single agent or in combination) in the order they were received will be collected and recorded in the eCRF to describe the study population. Start and stop dates, dose and schedule of the therapies, the prostate cancer disease state in which it was administered, and type of progression (i.e. biochemical [rising PSA], radiographic, and/or symptomatic) will be captured. Prior abiraterone therapy and details of disease progression, and subject's reason to forego chemotherapy will be collected in the Clinical database.

10.3. PSMA-avid Tumor Burden

PSMA tumor avidity based on ^{18}F-DCFPyL PET/CT imaging will be centrally assessed prior to randomization to increase homogeneity and optimize potential benefit without unnecessarily exposing subjects to I-131-1095 therapy. Baseline conventional imaging e.g., CT, MRI, bone scan will be used as a comparator reference to ensure adequate PSMA uptake to sites of disease. SUVs and lesion size will be documented for all subjects. All imaging studies will be sent to the central imaging core lab.

11. EFFICACY AND SAFETY VARIABLES

11.1. Assessment of Efficacy

11.1.1. PSA (total)

PSA (total) will be assessed at the central laboratory throughout the study at intervals defined in Section 7.6. Regardless of PSA values, study drug administration should continue until criteria in Section 8.3.2 is met. Throughout the study, PSA rise without evidence of radiographic progression is strongly discouraged as criteria to start a new systemic anti-cancer therapy.

11.1.2. Radiographic Assessments

Subjects will undergo CT/MRI, whole-body bone scans and ^{18}F-DCFPyL PET/CT at intervals noted in Section 7.6 or at any time progression is suspected. The assessment of radiographic response and progression will be performed by the investigator using RECIST 1.1 for measurable soft tissue disease on CT/MRI and PCWG3 for bone disease on bone scan. Only patients with either presentation at baseline will be included in the respective assessment. The same imaging modality should be used throughout the study for any given patient. Each site should designate an investigator or radiologist as the primary imaging reviewer to ensure that all images are read consistently according to RECIST 1.1 and PCWG3-modified RECIST 1.1, as specified by the protocol. Radiographic imaging is not required after radiographic progression has been confirmed and documented according to protocol specifications.

Total lesion PSMA expression will be calculated by multiplying tumor volume and the SUV.

11.1.2.1. Bone Scan

A radionuclide bone scan (either ^{99m}Tc or ^{18}F-NaF PET/CT, depending upon the site's standard of care) will be obtained at intervals noted in Section 7.6. If conducted as part of Screening, ^{18}F-NaF PET bone scans must be done at least five physical half-lives (10 hours) prior to ^{18}F-DCFPyL injection. Bone scans will be assessed by the Investigator for radiographic response and progression and be submitted to the Central Imaging Core Lab for PSMA avidity and aBSI assessments.

11.1.2.2. CT or MRI

A contrast-enhanced (if not contraindicated) CT or MRI of the abdomen and pelvis and a CT of the chest will be obtained at intervals noted in Section 7.6. High density oral contrast medium (oral water contrast is acceptable) cannot be administered within 5 days prior to study drug injection.

Study scans should be read on site and submitted to the central imaging core lab in DICOM format per instruction in the Imaging Manual to determine changes over time. See Section 11.1.3.1 for Radiographic Progression criteria and Section 11.1.3.2 for Clinical Progression criteria.

11.1.2.3. ^{18}F-DCFPyL PET Imaging

^{18}F-DCFPyL (PyL) PET/CT imaging will be performed at intervals defined in Section 7.6.

All PyL PET/CT scans should be submitted in DICOM format to the Central Imaging Core Lab to evaluate tumor PSMA avidity, total SUV measurements and PyL-positive lesion counts as applicable. Additional unscheduled ^{18}F-DCFPyL PET/CT scan(s) may be performed with Sponsor approval.

Prior to ^{18}F-DCFPyL dosing, all PET/CT scanners to be used in this study must be qualified in accordance with the procedures outlined in the Imaging Manual. Scans will be reviewed for quality assessment to ensure images were acquired in accordance with the protocol and other technical specifications in addition to confirming DICOM header data to ensure SUV accuracy.

11.1.2.4. Automated Bone Scan Index (aBSI)

Subject's whole body bone scans will be assessed by a Central Imaging Core Lab at intervals noted in Section 7.6 to determine changes over time. The Bone Scan Index (BSI) is defined as the percentage of total skeletal mass occupied by bone metastases. aBSI (automated BSI) is proprietary software for automatically and semi-automatically estimating BSI from whole-body planar bone scans.

11.1.3. Clinical Assessments Related to Prostate Cancer

11.1.3.1. Radiographic Progression

Radiographic progression of bone disease per PCWG3 is defined as the appearance of 2 or more new bone lesions on first post-treatment scan, with at least 2 additional new lesions seen on the next, confirmatory scan. If at least 2 additional new lesions are seen on the confirmatory scan, the date of progression is the date of the first post-treatment scan, when the first two new bone lesions were identified. For all other scans after the first post-treatment scan, progression is defined as the appearance of at least two new lesions when compared to the first post-treatment scan, and then confirmed on a subsequent scan. The date of progression is the date of the scan that first documents at least two new lesions.

Radiographic progression of nodal and visceral disease per PCWG3-modified RECIST 1.1 is defined as at least a 20% increase in the sum of diameters of target lesions, using the smallest sum on the study as reference. The sum of diameters of target lesions must also be an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.

The documentation required for the determination of radiographic disease progression is listed in Table 6 below.

Table 6: Protocol-specified Documentation for Radiographic Evidence of Disease Progression

Disease Progression Detected (Visit)	Criteria for Progression	Criteria for Confirmation of Progression
Week 9 (first post treatment scan)	Bone lesions: Detection of at least 2 new lesions on first post treatment scan compared to baseline. Nodal and visceral: Progressive disease on CT/MRI by RECIST 1.1	At least two new lesions seen on confirmatory scan (e.g. Week 17 scan) in addition to lesions seen on Week 9 bone scan. No confirmatory scan required for soft-tissue disease progression.
Week 17	Bone lesions: Detection of 2 or more new lesions compared to **Week 9** bone scan Soft-tissue lesions: Progressive disease on CT/MRI by RECIST 1.1	Timing: At least 6 weeks after progression identified, confirmation of the lesions seen at the Week 17 bone scan. No confirmatory scan required for soft-tissue disease progression.
Week 25	Bone lesions: 2 or more new lesions compared to **Week 9** bone scan Soft-tissue lesions: Progressive disease on CT/MRI by RECIST 1.1	Timing: At least 6 weeks after progression identified, confirmation of the lesions seen at the Week 25 bone scan. No confirmatory scan required for soft-tissue disease progression.
Week 36	Bone lesions: 2 or more new lesions compared to **Week 9** bone scan Soft-tissue lesions: Progressive disease on CT/MRI by RECIST 1.1	Timing: At least 6 weeks after progression identified, confirmation of the lesions seen at the Week 36 bone scan. No confirmatory scan required for soft-tissue disease progression.
Week 53 (EOS Visit)	Bone lesions: 2 or more new lesions compared to **Week 9** bone scan Soft-tissue lesions: Progressive disease on CT/MRI by RECIST 1.1	Timing: At least 6 weeks after progression identified, confirmation of the lesions seen at the Week 53 bone scan. No confirmatory scan required for soft-tissue disease progression.

11.1.3.2. Unequivocal Clinical Progression

Unequivocal clinical progression is defined when the subject is no longer deemed to be benefitting (NCLB) from treatment with I-131-1095 and any of the following occur:

a) new onset of prostate cancer pain requiring chronic opiate use (chronic opiate use (excluding acetaminophen-opiate fixed-dose combinations) will be considered as daily use for more than 7 consecutive days or more than 10 days within a 14-day period), or

b) deterioration of ECOG performance status to ≥ 3 as a result of prostate cancer, or

c) initiation of cytotoxic chemotherapy for prostate cancer, or

d) radiation therapy or surgical intervention because of complications of tumor progression. Palliative radiotherapy of symptoms due to prostate cancer will not be considered unequivocal progression and will not mandate study drug discontinuation

The corresponding NLCB reporting metric will be defined as the date and the specific reason(s) the I-131-1095 therapy is ultimately discontinued. This endpoint as proposed by PCWG3 permits individualized provider-patient decisions to continue or discontinue a treatment based on the primary therapeutic objective for which it is being administered and assessed, be it quality of life, PROs, or survival.[29]

11.1.3.3. Symptomatic Skeletal Event (SSE)

SSEs are defined as symptomatic pathologic fracture, radiation to the bone, or tumor-related orthopedic surgical intervention, or spinal cord compression. Asymptomatic fractures are skeletal-related events and not considered SSEs of clear clinical significance.[29] SSEs or the underlying indication for the event will be collected as Adverse Events (see Section 12.1.1)

11.1.3.4. Initiation of New Cytotoxic, Anti-neoplastic, or Investigational Treatment for Prostate Cancer

The assessment of new treatment for prostate cancer following I-131-1095 or enzalutamide therapy will be assessed throughout the duration of study until completion of the survival follow-up period. If a new cytotoxic, anti-neoplastic or investigational anticancer treatment is planned to initiate before 28 days after the last dose of I-131-1095 (treatment arm) or enzalutamide (control arm), then the End of Study Safety Visit should occur immediately before starting the new treatment.

11.1.4. Patient-Reported Outcomes (PROs)

All patient reported outcomes (PROs) will be completed by subjects at intervals defined in Section 7.6. PROs are source documents and as such, must be attributable to the subject completing the form(s). Listed below are the PROs used during this study.

11.1.4.1. Brief Pain Inventory –Short Form (BPI-SF)

The Brief Pain Inventory questionnaire is a validated instrument that is a patient self-rated scale assessing level of pain, effect of the pain on activities of daily living, and analgesic use. The short form of the Brief Pain Inventory (BPI-SF) is used in this study and contains nine main questions (See Appendix A).

11.1.4.2. Functional Assessment of Cancer Therapy –Prostate (FACT-P)

The FACT-P quality of life (QoL) questionnaire is a multi-dimensional, self-reported QoL instrument specifically designed for use with prostate cancer patients. It consists of 27 core items which assess patient function in four domains: physical, social/family, emotional, and functional well-being, which is further supplemented by 12 site-specific items to assess for prostate-related symptoms. Each item is rated on a 0 to 4 Likert-type scale, and then combined

to produce subscale scores for each domain, as well as a global quality of life score with higher scores representing better QoL. See Appendix B for the FACT-P questionnaire.

11.1.4.3. EQ-5Q-5L

The EQ-5D-5L consists of a 5-item questionnaire and the EQ Visual Analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. See Appendix D for the EQ-5D-5L.

11.1.4.4. SF-12v2 Health Survey

The SF-12v2 Health Survey is a 12-item general health survey which can be self-administered or interview-administered. The survey measures the eight health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health). Together these provide psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. See Appendix C for the SF-12v2 Health Survey.

11.1.5. Survival Status

The subject's survival status will be recorded at intervals defined in Section 7.6. If a subject discontinues from either arm of the study during the core efficacy period for any reason, they should remain on-study for follow-up survival status.

11.1.6. ECOG Status

ECOG performance status has a rating from 0-5 as defined in the Table below. ECOG status will be collected at intervals defined in Section 7.6 to evaluate changes from randomization to each subsequent timepoint.

Table 7: ECOG performance rating

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Death

11.2. Assessment of Safety

Throughout the study, the safety and tolerability of adjunct I-131-1095 will be assessed. An independent Data Monitoring Committee (iDMC) will monitor safety and efficacy data at pre-defined timepoints as noted in the DMC Charter.

11.2.1. Vital Signs

Vital signs (resting blood pressure in the sitting position, heart rate, and temperature) will be measured at intervals defined in Section 7.6. For those subjects randomized to enzalutamide plus I-131-1095, pre and post dosing vital signs will be measured within 4 hours of Study Drug Administration.

The Investigator will evaluate any worsening in vital signs for its clinical relevance and whether it meets the definition of an AE or SAE. Any changes determined to meet the definition of an AE or SAE will be recorded in the AE section of the CRF; an SAE form will be forwarded to Progenics' designee for all SAEs.

Height and weight will be measured at screening visit. For subjects that are randomized, weight will be measured at intervals defined in Section 7.6.

11.2.2. Physical Examination

A complete physical examination will be performed at screening. Brief physical examinations thereafter will be performed as detailed in Section 7.6.

- The **complete physical exam** will include head, ears, eyes, nose, mouth, skin, cardiac (heart), respiratory (lung), lymphatic/lymph nodes, genito-urinary, gastrointestinal, skeletal, and neurologic systems.
- The **brief physical exams** will be directed towards patient-reported symptoms and areas of prostate cancer spread, including cardiac, respiratory, lymphatic/lymph nodes, genito-urinary, gastrointestinal, and skeletal systems.

All relevant findings at screening will be recorded on the Medical History CRF. The Investigator will evaluate any worsening at the post-dose physical examination for clinical relevance and to determine whether an AE has occurred. Any changes determined to meet the definition of an AE or SAE will be recorded on the AE page of the CRF, and an SAER form will be forwarded to the Progenics' designee if applicable. Specific observations (signs), symptoms and/or laboratory information supporting these changes will also be documented.

11.2.3. Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed at Screening and End of TreatmentVisit. For those subjects who are randomized to I-131-1095, pre- and immediately post I-131-1095 treatment on Day(s) of Study Drug Administration, ECGs will also be performed, with the exception of Day 1 of the first therapeutic dosing cycle where ECG will be performed **post** dose only. ECGs will be obtained after the patient has rested quietly and awake in a fully supine position (or semi-recumbent, if supine not tolerated) for 5–10 minutes. Any clinically significant abnormalities in ECGs should be captured on the AE page of the eCRF. ECG parameters being assessed can be found in Section 13.2.5.3.

The investigator or designee will be responsible for the initial reading of ECGs prior to the subject being discharged from the clinic at each applicable visit. All ECGs must be submitted to the central ECG core lab and be read centrally. Please refer to the ECG Procedure Manual for acquisition and transmittal details.

11.2.4. Laboratory Assessments

Blood and urine samples for hematology, chemistry, thyroid hormones, testosterone, and anti-androgen receptor (AR-V7) immunohistochemistry will be collected at Screening and at the timepoints as described in Section 7.6 and Table 3 to monitor safety parameters. While central labs are drawn at Screening, local lab results may be used to determine eligibility with prior approval by the Sponsor. Patients who are scheduled to complete Day 1 > 30 days from when the Screening Hematology and/or Chemistry samples collected must have these laboratory assessments repeated to confirm that the patient still meets the associated entry criteria prior to receiving their first dose of randomized treatment.

All scheduled clinical laboratory tests will be performed and analyzed by a central laboratory for inclusion in the study database. All samples for central laboratory analysis must be collected, prepared, labeled, and shipped according to the laboratory's requirements. These labs may be collected by Home Healthcare Professionals as indicated in Section 7.6 and Table 3.

Abnormal labs that are assessed as clinically significant will be recorded on the AE page of the eCRF. If the labs meet any of the serious criteria outlined in Section 12, an SAE form should also be completed and submitted per the instructions on the SAE form.

In the event that unscheduled laboratory tests are locally collected a duplicate sample should be provided to the central laboratory when possible. If not possible to provide a sample for central analysis, only AEs associated with abnormal unscheduled local labs will be collected in the study database.

11.2.4.1. Subjects who are randomized to I-131-1095

- Blood samples for chemistry and hematology and urinalysis will be collected by site staff for central analysis on the day of dosing before administering the I-131-1095 dose to the subject (See Table 8 for specific analytes). An additional blood sample may be assessed locally to confirm subjects hematologic values have returned to baseline or levels no greater than CTCAE v5.0 Grade 1 before administering the I-131-1095 dose (See Section 7.7).
- Blood samples for chemistry and hematology will be drawn for central analysis every two weeks after I-131-1095 dosing for up to eight weeks after dosing (See Table 8 for specific analytes). If lab abnormalities resulting from administration of study drug are still Grade 2 or higher at eight weeks, Unscheduled laboratory assessments should continue to be followed weekly until recovery to baseline or CTCAE v5.0 Grade 1 or better.
- In addition to Screening and End of Study Visit (Week 53), subjects will be tested for evidence of hypothyroidism by measuring levels of TSH and Free T4. Thyroid hormones will be collected approximately every 4 weeks during treatment (See Table 8).

11.2.4.2. Subjects who are NOT randomized to I-131-1095

Safety labs for chemistry, hematology and urinalysis will be drawn at the timepoints as described in Table 3 for central analysis.

A detailed list of analytes is listed in Table 8.

Table 8: Clinical Laboratory Tests for Safety Assessments: Blood Chemistry, Hematology, Urinalysis, Thyroid Hormones*

Chemistry	Hematology	Thyroid	Urinalysis	Other
All subjects: *Screening and Weeks 1, 5, 7, 9, 13, 17, 21, 25, 29, 36, 42, 47, and 53*	*All subjects*: *Screening and Weeks 1, 5, 7, 9, 13, 17, 21, 25, 29, 36, 42, 47, and 53*	*All subjects: Screening and Week 53.*	*All subjects: Weeks 1, 9, 17, 25, 53*	*All subjects: Screening only*
For subjects dosed with I-131-1095 additional assessments at 2, 4, 6 and 8 weeks after dosing. (eg. Weeks 3, 11, 15, 19, 23, 27, 31)	*For subjects dosed with I-131-1095 additional assessments at 2, 4, 6 and 8 weeks after dosing. (eg. Weeks 3, 11, 15, 19, 23, 27, 31)*	*Additional assessments for subjects dosed with I-131-1095:* *Weeks 5, 9, 13, 17, 21, 25, 29, 36*		
Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen (BUN) Serum creatinine Glucose (non-fasting) Calcium Phosphate Magnesium Albumin Total Protein Alkaline Phosphatase (ALK) Lactate Dehydrogenase (LDH) Creatine Kinase (CK) Bilirubin, total Alanine Aminotransferase (ALT) Aspartate aminotransferase (AST)	White blood cell count (WBC) WBC differential Red blood cell count (RBC) Hemoglobin (Hgb) Hematocrit (Hct) Mean corpuscular volume Platelet count	TSH T4 (free)	pH Specific Gravity Protein Glucose Ketones Blood WBC/HPF RBC/HPF Crystals	Testosterone AR-V7

Chemistry	**Hematology**	**Thyroid**	**Urinalysis**	**Other**
All subjects: *Screening and Weeks 1, 5, 7, 9, 13, 17, 21, 25, 29, 36, 42, 47, and 53*	*All subjects*: *Screening and Weeks 1, 5, 7, 9, 13, 17, 21, 25, 29, 36, 42, 47, and 53*	*All subjects: Screening and Week 53.*	*All subjects: Weeks 1, 9, 17, 25, 53*	*All subjects: Screening only*
For subjects dosed with I-131-1095 additional assessments at 2, 4, 6 and 8 weeks after dosing. (eg. Weeks 3, 11, 15, 19, 23, 27, 31)	*For subjects dosed with I-131-1095 additional assessments at 2, 4, 6 and 8 weeks after dosing. (eg. Weeks 3, 11, 15, 19, 23, 27, 31)*	*Additional assessments for subjects dosed with I-131-1095:* *Weeks 5, 9, 13, 17, 21, 25, 29, 36*		

*If collected on the day of I-131-1095 dosing, labs must be drawn **before** dosing.

†Creatinine clearance will be calculated by the central laboratory.

12. REPORTING SAFETY INFORMATION

The site staff will screen subjects for adverse events during scheduled and non-scheduled visits.

12.1. Adverse Events

12.1.1. Definition of Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a research subject administered an investigational product (IP) at any dose, which does not necessarily have a causal relationship with the IP.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptoms or disease, or exacerbation of existing disease temporally associated with the use of the IP, whether or not considered related to the IP. Abnormal laboratory results should be considered AEs if they are associated with clinical signs and symptoms or have clinical significance, i.e. result in discontinuation or delay in dosing of study drug, initiates a diagnostic work-up, or requires intervention, i.e. transfusion. The latest, current version of the Medical Dictionary for Regulatory Activities (MedDRA), Version 23 will be used by the Sponsor to code AEs. "Disease progression" itself should not be reported as an AE. It is anticipated that a proportion of subjects will experience disease progression in this study. When clinical disease progression is identified, the clinical event which marks or identifies the disease progression should be reported as the AE term for standard AE reporting, including serious adverse event (SAE) reporting. Symptomatic skeletal-related events (SSEs), as defined in Section 11.1.3.3, or the underlying indication for the event will be collected as AEs.

All AEs must be recorded according to Section 12.1.2.

12.1.2. Definition of Serious Adverse Event (AE)

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

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect of a patient's child

It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

12.1.3. Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is a serious or non-serious event of scientific and medical concern specific to I-131-1095 occurring during the Survival Follow-up Period regardless of causality. AESIs defined for this study include:

- secondary malignancies e.g., myelodysplastic syndrome (MDS), Acute Myeloid Leukemia (AML)

- thyroid disorders e.g., hypo- or hyperthyroidism

CTCAE v5.0, Grade 3 or 4 for the following:

- Xerostomia
- Xerophthalmia
- Renal dysfunction
- Renal failure
- Creatinine increased
- Acute kidney injury
- Hepatic dysfunction
- Hepatic failure
- Alanine aminotransferase increase
- Aspartate aminotransferase increase

The events above are the ONLY AEs that will be collected and assessed during the Survival Period. If any of these events occur during the Randomized Treatment Period, they are to be collected as stated in section 12.1.1.

Regardless of seriousness, all AESIs should be recorded on the AE page of the eCRF *as well as* on the SAE/AESI form. Non-serious AESIs will be forwarded to the Sponsor or designee within 72 hours of first becoming aware of the event; serious AESIs will be forwarded within 24 hours of first becoming aware of the event. AESI collection starts at the beginning of the Survival Follow-up phase for at least one year or to the end of the study (whichever is later). AESI collection ends with the subject's death, lost to follow-up, initiation of anti-cancer therapy or withdrawal of consent.

12.2. Relationship to Study Drug

The Principal Investigator or Sub-Investigator must make the determination of the causal relationship (i.e. definitely related, possibly related, unlikely related, unrelated) between each AE and I-131-1095, enzalutamide and ^{18}F-DCFPyL, regardless of which treatment arm the subject has been randomized assigned. If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product (I-131-1095), enzalutamide or ^{18}F-DCFPyL, the AE should be considered "definitely or possibly related." If no valid reason exists for suggesting a relationship, then the AE should be classified as "unlikely related or unrelated." For any (S)AE occurring outside 24 hours of ^{18}F-DCFPyL administration, the relationship should be marked as "Not Applicable".

12.3. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation, will be recorded on the AE page of the eCRF within five days after becoming aware of the event.

During the screening period, the only AE/SAEs that will be collected for ^{18}F-DCFPyL are those that occur within 24 hours of ^{18}F-DCFPyL administration. During the Randomized treatment period, AEs/SAEs collection will begin post randomization after the first administration of I-131-1095 or enzalutamide and will continue until the end of the Randomized Treatment Period. The collection period for AESIs is extended through the Survival Follow up Period regardless of whether these events are serious or not. All AEs should be recorded on the AE page of the eCRF; an SAE form should also be completed for any AE that fits the serious criteria as defined in Section 12.1.2.

The AE term should be reported in standard medical terminology and be a medical diagnosis whenever possible. For each AE, the investigator will evaluate and report the onset date, resolution date, intensity, causality, action taken with I-131-1095/enzalutamide/^{18}F-DCFPyL , outcome, and whether or not the AE caused the patient to discontinue IP, enzalutamide or ^{18}F-DCFPyL and/or the study.

12.4. Severity

Severity (Intensity) will be assessed according to NCI CTCAE v.5.0. If the CTCAE grading is not defined in the NCI CTCAE grading table for a particular AE, severity will be rated according to the following definitions

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

It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.1.2. An AE of severe intensity may not be considered serious. Conversely, a serious AE can be of mild or moderate intensity.

12.5. Reporting Serious Adverse Events (SAEs)

All SAEs (related and unrelated) will be recorded on the AE page of the eCRF as well as on an SAE form, at the same interval defined for AE collection as indicated in Section 12.3. SAEs should be forwarded via phone, fax or email to the Sponsor or designee within 24 hours of becoming aware of the event. Medical records should not be provided unless specifically requested, as all relevant information should be provided on the SAE Report Form. The SAE form must be *signed and dated* by the Investigator. The original copy must remain on site with the CRF.

A new follow-up SAE form will be completed by the Investigator if significant follow-up information (i.e., diagnosis, outcome, causality assessment, results of specific investigations) becomes available after submission of the initial form. The follow up SAE form must be *signed* and dated by the Investigator. The follow-up form and any additional source documentation regarding the event will be sent to Progenics, or designee, as described above. In addition to the

AE reporting period stated in Section 12.3, any SAEs considered at least *possibly related* to the investigational product and discovered by the Investigator at any time *after* the protocol-defined reporting period, should be reported to the Sponsor or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE form, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by email or fax to Sponsor, or designee. Subjects with SAEs must be followed until the event resolves, the event or sequelae stabilizes, or it is unlikely that additional information can be obtained after due diligence with follow-up efforts (i.e. the subject or investigator is unable to provide additional information), or the subject is lost to follow-up.

Additional follow-up information, if required or available, should promptly be emailed or faxed to Sponsor, or designee, via a *signed and dated* follow-up SAE form, within 24 hours of first becoming aware of the additional information.

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

12.6. Partner Pregnancy

Should a pregnancy occur in a subject's partner, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE, but the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the male subject was discontinued from the study. All reports of congenital abnormalities/birth defects and spontaneous miscarriages are considered SAEs and will be processed according to Section 12.5. Elective abortions without complications should not be handled as AEs. In order to collect information surrounding the pregnancy, the subject's female partner will be consented with a pregnancy focused ICF.

13. STATISTICS

A Statistical Analysis Plan (SAP) will describe the details that go into the endpoints, the statistical methods, and the analyses planned for this study. In general, all continuous variables will be summarized showing the N, mean, median, standard deviation, minimum and maximum values. Discrete variables will be presented showing the N and percentage. Summaries will be presented by treatment group.

13.1. Sample Size Determination

The primary endpoint of the first occurrence of at least a 50% decrease in PSA from baseline, confirmed by a second measurement at least 3 weeks later will assume a response rate of 30%[21] for enzalutamide alone and a response of 59% for I-131-1095 plus enzalutamide. Based on 2-sided chi-squared test with alpha = 0.05, and 2:1 randomization ratio, a minimum of 102 (34 for enzalutamide alone and 64 for enzalutamide plus I-131-1095 group) subjects will be required to provide 80% power; with an estimated drop-out rate of 15%, a total of 120 subjects will be randomized (40 randomized to enzalutamide and 80 randomized to enzalutamide plus I-131-1095).

13.1.1. Analysis Populations

13.1.1.1. Full Analysis Set (FAS)

The FAS follows the ITT principles defined in ICH-E9[40] and is defined as all randomized subjects and will be analyzed according to the treatment as randomized. The FAS will be used for all efficacy analyses and baseline parameters; the primary efficacy conclusion will be based on the result of this analysis.

13.1.1.2. Per-Protocol (PP) Set

The PP Set will consist of the FAS excluding subjects with major protocol violations, subjects who did not receive at least one dose of study treatment or who did not complete at least one post-baseline PSA assessment. If a subject received at least 1 dose of I-131-1095 then the subject is assigned to the I-131-1095 group, otherwise treatment assignment is per the randomization. The PP analysis of the primary endpoint will be used as one of the sensitivity analyses.

13.1.1.3. Safety Set

The safety set is defined as all subjects who received any dose of study drug defined as ^{18}F-DCFPyL, I-131-1095 and Enzalutamide. Any subject who received any amount of I-131-1095 will be assigned to the I-131-1095 treatment group. The safety set will be used for the safety and baseline parameters.

13.2. Statistical Analysis

13.2.1. Missing Data

Multiple imputations will be used to impute missing post-baseline values for the primary endpoint. The details of this method will be described in the SAP. There is no plan to impute missing data for any other endpoints.

13.2.2. Baseline Characteristics

13.2.2.1. Subject Disposition

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

13.2.2.2. Demographics and Baseline Characteristics

Baseline characteristics, including medical history coded using MedDRA, will be summarized for the efficacy and safety patient population sets. The PP set may also be presented for some of these assessments.

13.2.2.3. Prior and Concomitant Medications and Procedures

Concomitant medications, coded using the current version of the World Health Organization (WHO) Drug Dictionary at the start of the study, will be tabulated. A concomitant medication is one administered post- I-131-1095 and/or enzalutamide dosing through the end of the core efficacy period. New anti-cancer therapies will be collected as concomitant medications in the survival follow-up period.

Prior medications and procedures will also be tabulated. Procedures will be coded using the same version of MedDRA used for coding medical history.

13.2.3. Efficacy Analyses

13.2.3.1. Primary Endpoint Analysis – PSA Response

The analysis of the primary endpoint as defined in Section 7.2.1 will be performed using a 2-sided Cochran-Mantel-Haenszel chi-squared test based on FAS population stratified by baseline risk category to compare the two treatment groups in PSA reduction of at least 50% from baseline as confirmed by a second PSA assessment at least 3 weeks later; the efficacy conclusion will be based on the result of this analysis. Missing data will be imputed using multiple imputation approach assuming missing-at-random. If more than 20% of the expected cell frequencies are less than 5, then a 2-sided Fisher's exact test will be performed instead.

A sensitivity analysis will be performed similarly, but a PSA reduction of at least 50% from baseline can be confirmed at any point after the first reduction.

The analysis of the primary endpoint using the PP set will be performed as one of the sensitivity analyses. Additional sensitivity analysis of the primary endpoint based on FAS may be performed following different approaches for handling missing data.

The details of the analyses will be described in a separate analysis plan.

13.2.3.2. Secondary Endpoints Analyses

All secondary endpoints as defined in Section 7.2.2 will be analyzed for the FAS set.

The endpoint of overall response rate will be analyzed using a 2-sided chi-squared test based on a type I error of 0.05 to compare the two treatment groups. If more than 20% of the expected cell frequencies are less than 5, then a 2-sided Fisher's exact test will be used.

The following time to event endpoints will be analyzed using 2-sided log rank test stratified by baseline risk category based on type I error of 0.05; subjects who will be censored at the date of early withdrawal or the final study date whichever is earlier. Study termination criteria are defined in Section 7.9. Kaplan-Meier plots will also be presented along with median survival times within each treatment group as well as 2-sided 95% confidence intervals.

- OS defined as time from randomization to death or last date confirmed alive
- PSA progression defined as time from randomization to date of first confirmed PSA progression value.
- rPFS defined as time from randomization to the first occurrence of radiographic progression based on RECIST 1.1 for soft tissue or PCWG3-modified RECIST 1.1 for bone, or death from any cause
- Duration of response defined as time from first date of CR or PR to date of disease progression
- Time to next treatment defined as the time from randomization to initiation of any new treatment for prostate cancer

13.2.3.3. Exploratory Endpoints Analyses

All exploratory endpoints as defined in Section 7.2.3 will be analyzed based on the FAS set.

The rate of pain progression defined from BPI-SF will be analyzed using a 2-sided chi-squared test based on a type I error of 0.05 to compare the proportions between treatment groups. If more than 20% of the expected cell frequencies are less than 5, then a 2-sided Fisher's exact test will be performed instead.

The following continuous endpoints will be transformed into a scale between 0-100; normality of the data will be tested based on a Shapiro-Wilk test; if normality is assumed, a repeated measures analysis of variance will be used to evaluate the treatment difference; otherwise, a generalized test will be performed. The aBSI and ECOG performance status scores will not be transformed.

- ^{18}F-DCFPyL uptake defined by SUVmax
- ^{18}F-DCFPyL positive lesion counts
- Overall score from FACT-P
- The physical domain from FACT-P
- The social/family domain from FACT-P

- The emotional domain from FACT-P
- The physical domain from FACT-P
- The functional/well-being domain from FACT-P
- The SF-12v2 Physical Component Summary (PCS) score
- The SF-12v2 Mental Component Summary (MCS) score
- aBSI scores
- ECOG performance status ratings

The endpoint of time from randomization to first symptomatic skeletal event (SSE) will be analyzed using a 2-sided log rank test with a type I error of 0.05 to compare the two groups.

The endpoint of EQ-5D-5L VAS and index values will be compared between treatment groups.

13.2.4. Interim Analysis for Efficacy

An interim analysis for efficacy will be performed to evaluate the predictive probability of attaining the primary efficacy endpoint at the end of the study when all subjects complete the Randomized Treatment Period up to 12 months following their first dose of I-131-1095 and/or enzalutamide, based on the data observed at the interim analysis. Overall survival and rPFS will also be calculated for both treatment groups.

The interim analysis will be performed when there are at least 48 evaluable subjects contributing PSA results with approximately three months of follow-up. The data will be evaluated with regard to randomized treatment to calculate the Bayesian predictive probability of the primary endpoint based on the observed data. The interim analysis will be performed through an independent contract research organization.

The iDMC will review the results of the interim analysis and will address whether the criterion for the predictive probability of success in the primary efficacy endpoint has been met. The iDMC will provide the Sponsor's management with a recommendation regarding the continuation or stopping of the study.

The DMC will review the results of the analysis with regards to stopping the study either for futility or for success of I-131-1095 plus enzalutamide against enzalutamide alone. The stopping boundary for futility is a predictive probability of success below 30%, which approximately corresponds with a difference of less than 10% in response rates between treatments for the primary endpoint of PSA decline of ≥50%. If this boundary is crossed, the iDMC will recommend termination of the study for futility. If the predictive probability of success is greater than 90%, which approximately corresponds with a difference of greater than 35% in response rates between treatments for the primary endpoint, the iDMC will contact the Sponsor's management to consider terminating the study for efficacy. This recommendation is non-binding and will lead to discussions regarding stopping the study. If neither the futility nor the efficacy boundaries are crossed, then the iDMC will recommend the study continue without modification.

The results of the interim analysis will not be shared with anyone outside the DMC while the trial is ongoing. The study team and the subjects will remain masked to treatments until the end of the study, unless justified unblinding is required due to safety considerations. Since the study

is not intended to be stopped for efficacy at the interim analysis, there will be no alpha adjustment for the primary study analysis.

13.2.5. Safety Analyses

All Safety endpoints will be presented for the safety set and summarized by treatment group. Tabular summaries will include the incidence overall (number and percentage of patients with events classified by system organ class and preferred term) as well as incidence by intensity, causality, and outcome (e.g. leading to discontinuation of study drug).

Patients with the same adverse event reported more than once will be counted once at the maximum severity or strongest relationship to study drug.

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

13.2.5.1. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and temperature will be summarized at baseline and at each subsequent scheduled assessment timepoint by treatment group. Change from baseline in each vital sign parameter will be presented for each post-dose visit by treatment group. Potentially clinically significant vital signs abnormalities and change from baseline in weight will also be presented.

13.2.5.2. Physical Examination

Physical exam findings and patient reported symptoms and areas of prostate cancer spread will be summarized by treatment groups and visit. If the findings are noted as study entry, the details will be summarized as medical or prostate cancer history. Any changes in physical exam findings after treatment has begun will be considered as adverse events.

13.2.5.3. ECGs

Results from the central ECG laboratory collected during the treatment period will be presented. At each time point the central reviewer's assessment of the ECG (normal, borderline or abnormal) and heart rate, duration of QRS complex, RR, PR and QT intervals will be summarized. QTcF (Fridericia) and QTcB (Bazett) will be calculated programmatically using the reported ECG values (RR and QT). For triplicate ECGs, the mean of the three ECG assessments will be used to determine the values at that time point.

13.2.5.4. Laboratory Assessments

Laboratory data consist of hematology, urinalysis, and chemistry laboratory tests. The National Cancer Institute's CTCAE, version 5.0, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus postbaseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based on the normal range (low, normal, and high) will be provided for each parameter to summarize baseline result versus postbaseline result. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of study drug.

Change from baseline in hematology, clinical chemistry and thyroid hormones (for those subjects treated with I-131-1095) variables will be calculated for each post-dose visit on treatment.

CTCAE grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of lab result to corresponding SI units. The following parameters have CTC grades defined for both high and low values:

- Potassium, sodium, magnesium and calcium (corrected), so high and low CTC grades will be calculated. CTC grades are not defined for Total protein, Urea, Absolute eosinophil count, Absolute basophil count, or Absolute monocyte count.

13.2.5.5. Concomitant Medications

Concomitant medications will be summarized by ATC level 4 and preferred term between treatment groups.

13.2.6. Other Analyses

13.2.6.1. Exposure

The dose and cumulative dose of enzalutamide (mg) and I-131-1095 will be summarized with descriptive statistics including n, mean, standard deviation, median and range.

13.2.6.2. Treatment Compliance

Treatment compliance will be measured for both treatment groups, estimating the percentage of expected doses received over the duration of the trial that the subject is enrolled for and again for the full duration of the trial.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Data collected during this study may be used to support the development, registration or marketing of I-131-1095 Injection. All data collected during the study will be controlled by Progenics or designee and Progenics will abide by all relevant data protection laws.

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

14.1. Study Monitoring

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

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

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

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

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

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements.

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Progenics or designee may conduct a quality assurance audit. Please see Section 14.2 for details regarding the audit process.

16. ETHICS

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

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

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

16.2. Ethical Review: Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

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

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

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

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

16.3. Written Informed Consent

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

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

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

16.4. Subject Confidentiality

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

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

16.5. Financial Disclosure

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Case Report Forms and Study Records

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

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

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

17.2. Inspection of Records

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

17.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of two (2) years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation or as per local regulations, whichever is longer in duration. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records. No study document should be destroyed without prior written agreement between Sponsor and the investigator.

18. PUBLICATION POLICY

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

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

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

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20. APPENDICES

APPENDIX A. BRIEF PAIN INVENTORY-SHORT FORM (BPI-SF)

1095-2301 ARROW			
Study Number	**Site / Participant ID** XXX-XXX	**Visit Number**	**Visit Date** (dd-MMM-yyyy)

Brief Pain Inventory (BPI)

The **Brief Pain Inventory (BPI)** has become one of the most widely used measurement tools for assessing clinical pain. The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. This assessment should be completed by the study participant.

Participant Initials and Date:_____

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

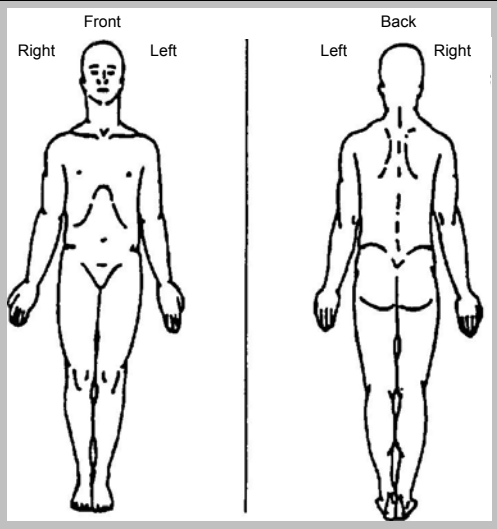
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

STUDY ID #:__________ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: __________

Date: ____/____/____ Time: ________

Name: _________________ _________________ ______________

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much **relief** you have received.

0% No Relief	10%	20%	30%	40%	50%	60%	70%	80%	90%	100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

B. Mood

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

C. Walking Ability

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

E. Relations with other people

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

F. Sleep

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

G. Enjoyment of life

0 Does not Interfere	1	2	3	4	5	6	7	8	9	10 Completely Interferes

APPENDIX B. FUNCTIONAL ASSESSMENT OF CANCER THERAPY – PROSTATE (FACT-P) (VERSION 4)

1095-2301 ARROW

Study Number	Site / Participant ID XXX-XXX	Visit Number	Visit Date (dd-MMM-yyyy)

FACT-P (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

FACT-P (Version 4)

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-P (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Participant First and Last Name (Please Print):_____

Signature of Participant

Date of Signature

APPENDIX C. SF-12 V2

1095-2301 ARROW			
Study Number	**Site / Participant ID** XXX-XXX	**Visit Number**	**Visit Date** (dd-MMM-yyyy)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Participant First and Last Name (Please Print):_____

Signature of Participant

Date of Signature

APPENDIX D. EQ-5D-5L

1095-2301 ARROW			
Study Number	**Site / Participant ID** XXX-XXX	**Visit Number**	**Visit Date** (dd-MMM-yyyy)

Health Questionnaire

English version for the USA

Participant First and Last Name (Please Print):_____

Signature of Participant	**Date of Signature**

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐