STATISTICAL ANALYSIS PLAN
PHASE II

VERSION: 3.0

DATE OF PLAN:

July 03, 2023

BASED ON:

Protocol Amendment 5: 29 June 2023

CRF 31 Aug 2021

STUDY DRUG:

I-131-1095

PROTOCOL NUMBER:

1095-2301

STUDY TITLE:

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)

SPONSOR:

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

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

Table 1: List of Abbreviations and Definitions

Abbreviation	Term
aBSI	automated Bone Scan Index
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
BPI-SF	Brief Pain Inventory-Short Form
cGy	centigray
CR	Complete Response
CRF	Case Report Form
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CRPC	Castration-resistant prostate cancer
CSR	Clinical Study Report
DDR	DNA damage response
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EEC	Efficacy Evaluation Committee
ECG	Electrocardiogram
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FAS	Full Analysis Set
GCP	Good Clinical Practice
Gy	Gray: Derived unit of ionizing radiation dose in the International System of Units; defined as the absorption of one joule of radiation energy per kilogram of matter
Hgb	Hemoglobin
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDMC	Independent Data Monitoring Committee
MAR	Missing-at-Random
MBq	Megabecquerel
mCi	Millicurie
MCMC	Monte-Carlo Markov Chain

mCRPC	Metastatic castration-resistant prostate cancer
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
N	Total Sample Size
ORR	Objective Response Rate
OS	Overall Survival
PCS	Physical Component Summary
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PP	Per-Protocol Population
PR	Partial Response
PSA	Prostate-Specific Antigen
PSMA	Prostate-Specific Membrane Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic Progression-Free Survival
SD	Standard Deviation
SAE	Serious Adverse Event
SAS	SAS® Software
SF-12	12-Item Short Form Health Survey
SUV_{max}	Maximum Standardized Uptake Value
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO DDE	World Health Organization Drug Dictionary Enhanced

2. CHANGES FROM THE PROTOCOL OR PREVIOUS VERSION OF THE STATISTICAL ANALYSIS PLAN

2.1. Changes from Previous Version of the Statistical Analysis Plan

- Remove Exploratory objective "To assess the association between the estimated tumor lesion absorbed radiation doses of I-131- 1095, SUVmax of the initial 18F-DCFPyL PET/CT scan and tumor response" and corresponding endpoint.

3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol 1095-2301 Amendment 5 dated 03 July 2023 and the Case Report Form (CRF) dated 31Aug 2021.

Protocol Versions and Dates:

- Original: 05 Dec 2018
- Amendment 1: 06 Feb 2019
- Amendment 2.2: 25 Nov 2019
- Amendment 3: 23 Apr 2021
- Amendment 4: 28 Feb 2022
- Amendment 5: 29 June 2023

This SAP was developed in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9[1] guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to Database lock of the study data. Further information can be found in the protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Efficacy Objective

To determine the efficacy of I-131-1095 combined with enzalutamide compared to enzalutamide alone assessed by prostate-specific antigen (PSA) response rate according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3)[2] criteria.

4.1.2. Secondary Efficacy Objectives

- To determine the radiographic response of I-131-1095 combined with enzalutamide compared to enzalutamide alone based on PCWG3-modified Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria[2, 3]
- 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

4.1.3. Exploratory Efficacy Objectives

- To determine the effect of I-131-1095 combined with enzalutamide compared to enzalutamide alone on prostate-specific membrane antigen (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 the incidence of 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 Eastern Cooperative Oncology Group (ECOG) performance status from baseline

4.1.4. Safety Objectives

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

4.2. Efficacy Endpoints

4.2.1. Primary Endpoint

PSA response rate 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.

4.2.2. Secondary Endpoints

- Objective response rate (ORR) from Baseline to the final assessment defined as the proportion of patients who have a partial response (PR) or complete response (CR) based on RECIST 1.1[3] for soft tissue or PCWG3[2] 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[2]
- Duration of response defined as the time from the first date of complete or PR to the first occurrence of radiographic progression based on PCWG3-modified RECIST 1.1, or unequivocal clinical progression as defined progression (Section 11.1.3.2 from Study Protocol).
- Time to next treatment defined as the time from randomization to initiation of any new treatment of prostate cancer

4.2.3. 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 SSE defined as symptomatic fracture, radiation or surgery to the bone, or spinal cord compression
- The incidence of pain progression, defined as an increase of ≥30% from baseline in the Brief Pain Inventory-Short Form (BPI-SF)[4] pain intensity score at 6 months
- Overall and component scores of the Functional Assessment of Cancer Therapy-Prostate (FACT-P)[5] questionnaire
- SF-12v2 domain scores, Physical Component Summary (PCS) scores and Mental Component Summary (MCS) scores
- Summary statistics for the EQ-5D-5L Visual Analogue Scale (VAS)

- Summary statistics for the EQ-5D-5L index
- aBSI scores
- ECOG performance status

5. STUDY DESIGN

5.1. Summary of 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), although treatment with taxane-based chemotherapy during hormone sensitive periods is allowed and must be ineligible or refuse to receive chemotherapy at time of consent. Enzalutamide will be prescribed as standard of care therapy 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 versus high risk prostate cancer [PCa]; see Section 7.4 from Study Protocol). 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 PSA data for at least 3 months following the first dose of randomized treatment (I-131-1095 or enzalutamide).

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/ magnetic resonance imaging (MRI), bone scan and ^{18}F-DCFPyL-PET, aBSI, SSE, survival status, and patient reported outcomes (PROs). The consensus guidelines of the RECIST, version 1.1 (RECIST 1.1) and the 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 adverse events (AEs), monitoring of vital signs and physical examinations, safety laboratory tests, and electrocardiograms (ECGs).

Patients may discontinue early from the Randomized Treatment Period but should 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 until the end of the study, whichever is later.

5.2. Definition of Study Drugs

There will be 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 in subjects randomized to treatment with I-131-1095. 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.

5.3. Randomization

The Randomization and Trial Supply Management (RTSM) system in RAVE will randomize eligible subjects to treatment group based on one of 2 risk strata determined from the results of three separate laboratory tests. Within each of these risk strata, subjects will be randomized (2:1) to receive I-131-1095 plus enzalutamide (N=80) or enzalutamide alone (N=40).

- Intermediate risk PCa: hemoglobin (Hgb) ≥11 g/dL **and** lactate dehydrogenase (LDH) <262 IU/L **and** alkaline phosphatase (ALP) <414 IU/L
- High-risk PCa: Hgb <11 g/dL or LDH ≥ 262 IU/L or ALP ≥ 414 IU/L

5.4. Clinical Assessments

Table 2: Scheduled Clinical Assessment Visits

All subjects, on-site visit	Screening Period		Randomized Treatment Period																				Survival follow-up[n] Period			
All subjects, home visit option																										
I-131-1095 arm only, home visit option			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				

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]
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	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→				

All subjects, on-site visit	Screening Period		Randomized Treatment Period																				Survival follow-up[n] Period			
All subjects, home visit option																										
I-131-1095 arm only, home visit option			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]
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

6. SAMPLE SIZE

6.1. Sample Size Justification and Calculation

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%[6] for enzalutamide alone and a response of 59% for I-131-1095 plus enzalutamide, estimated from results of an investigator-sponsored trial of I-131-1095 and literature reports for Lu-177. This shows a clinically meaningful difference of 29%.

$$H_0: \pi_{enza} = \pi_{1095+enzaby}$$

$$H_a: \pi_{enza} \neq \pi_{1095+enza}$$

Based on a 2-sided chi-squared test with alpha = 0.05, and 2:1 randomization ratio, a minimum of 102 (34 for enzalutamide alone and 68 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).

6.2. Sample Size Re-estimation

No sample size re-estimation will be performed for this study.

7. PLANNED INTERIM ANALYSES

One interim analysis is planned to evaluate the predictive probability of attaining the primary efficacy endpoint at the end of the randomized treatment period when all subjects complete the randomized treatment period up to 12 months after their first dose of I-131-1095 and/or enzalutamide, based on the data observed at the interim analysis. The primary efficacy endpoint (percent of subjects with at least a 50% reduction from baseline PSA) will be evaluated with respect to the predictive probability of success. Radiographic progression-free survival and OS by randomized treatment group will also be evaluated.

The interim analysis will be performed when there are at least 48 evaluable subjects available with at least three months of observation following the first dose of randomized treatment. The data will be unmasked to evaluate the predictive probability of a positive primary outcome based on the observed data at the interim analysis. The unmasking of the randomization and interim analysis will be performed through an independent contract research organization (CRO) who are not involved in other study activities.

To review the interim analysis result, the independent DMC (iDMC) will be responsible to address whether the criterion for the Bayesian predictive probability of success in the primary efficacy endpoint has been met after accounting for the comparability of the treatment groups. The iDMC will consider the clinical and statistical comparability of the two groups at the interim analysis - in light of the calculated predictive power[7] and the decision rule (Section 7.2), and will provide a designee from the Sponsor's management, who has no involvement in the trial's activities, with a recommendation regarding the continuation or stopping of the study.

The unmasked data and results of the interim analysis will not be shared with anyone outside of the iDMC with the exception of the sponsor contact designated for disclosure 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.

When all the subjects have completed the required observation period, a summary of only the primary endpoint (percentage of responders with a $\geq$ 50% decrease in PSA), overall survival and rPFS by randomized treatment group will be presented with respect to efficacy data. The analyses will be performed by the statistician independent of the study team. Subject-level data will remain masked, since the subjects are still being followed for long-term survival endpoints. Therefore, detailed listings for each subject will not be provided to the iDMC unless safety considerations justify breaking the randomization code for individual subjects. Safety data will be presented for safety monitoring in accordance with the iDMC charter. The summaries of safety data will be created by the statistician responsible for the overall analyses of study data.

At the end of the study, a full study report will be provided to the Sponsor including detailed listings by subject. At this time all data will be unmasked and analyses of all study endpoints will be performed.

7.1. Significance Level

The primary purpose of the interim analysis is to assess the futility of the study; efficacy endpoints will not be formally tested and the study is not expected to be terminated for efficacy; therefore the overall α level of the primary efficacy analysis will not be adjusted. The details of the statistical decision rules are described in the following section.

7.2. Statistical Considerations for the Interim Analysis

Formal statistical testing will not be performed to make any efficacy claims, only Bayesian predictive power[7] and the predictive probability of a positive study will be assessed at the interim analysis.

The Bayesian predictive power is the posterior probability that the proportions of PSA responders (defined as the subjects with PSA reduction of 50% of more according to PCWG3 criteria defined, confirmed by a second measurement at least 3 weeks later) is greater in the enzalutamide plus I-131-1095 group as compared to the enzalutamide alone group, based on the observed data at the interim, without any prior information of the response rates in the two groups.

The study will be terminated for futility if the predictive power based on the interim analysis does not indicate a "good probability" of success, defined as a predictive power of at least 30%. A non-binding threshold to terminate the study for overwhelming efficacy is set at 90%, but the study is not expected to be terminated for overwhelming efficacy. Otherwise, the study will continue.

The threshold of the predictive power described in the decision rules above will be communicated to the iDMC, as this information can be considered as part of the results of the interim analysis.

7.2.1. Analysis Set for Interim Analysis

The predictive power will be calculated on patients within the full analysis set (FAS) for the interim analysis (see Section 8.2.3 for the definition of the analysis set).

7.2.2. Handling of Missing Values

Missing values for efficacy endpoints will not be imputed for the interim analysis. The analysis will be performed using all reported data.

7.2.3. Statistical Methodology for the Interim Analysis

7.2.3.1. Calculation of Predictive Power

To calculate the predictive power, the success rates in the two treatment groups are assumed to have a non-informative prior, *Uniform*(*0*,*1*) is considered, which can also be written as $Beta(\gamma_i, \beta_i)$, where $\gamma_i = 1$ and $\beta_i = 1$ for *i*=1 and 2 (enzalutamide plus I-131-1095 group or the enzalutamide alone group). The numbers of successes (subjects with confirmed PSA reduction of 50% of more) from treatment group *i* before and after the interim look is denoted by s_i and t_i;

the total numbers of subjects in treatment group *i* before the interim look is denoted by n_i and the overall number of subjects in the treatment group *i* (including subjects before and after interim look) is denoted by N_i:

$$p_i \sim Beta(1,1)$$

$$s_i \mid p_i \sim Binom(n_i, p_i)$$

Then, the predicted probability of the future success, count T_i for treatment *i* conditional upon $S_i = s_i$ follows a *Binomial-Beta* distribution:

$$\tilde{p}(t_i \mid s_i) \sim \frac{Beta(s_i + t_i + 1, N_i - s_i - t_i + 1)}{(N_i - n_i - t_i)Beta(t_i + 1, N_i - n_i - t_i)Beta(s_i + 1, n_i - s_i + 1)}$$

Therefore, the predictive power will have the following form:

$$P(n, \eta, \delta) = \sum_{t_1=0}^{N_1-n_1} \sum_{t_2=0}^{N_2-n_2} I\{P(d(p_1^*, p_2^*) > \delta) > \eta \mid X_{(N)}\} \times \tilde{p}(t_1 \mid s_1) \times \tilde{p}(t_2 \mid s_2),$$

where p_i^* denotes the posterior event rate in treatment group *i* conditional on $S_i = s_i$ and $T_i = t_i$, where

$$p_i^* \mid t_i, s_i \sim Beta(s_i + t_i + 1, N_i - s_i - t_i + 1);$$

and $d(p_1^*, p_2^*)$ is the difference of the posterior event rate between the treatment groups; δ is the clinically significant treatment difference.

When $N = N_1 = N_2$ is large, the predictive power is equivalent to the following:

$$P(n, \alpha, \delta) = \sum_{t_1=0}^{N_1-n_1} \sum_{t_2=0}^{N_2-n_2} I\{Z_N > z_{1-a} \mid s_1, s_2, t_1, t_2\} \times \tilde{p}(t_1 \mid s_1) \times \tilde{p}(t_2 \mid s_2),$$

where Z_N is the z-statistic for comparing the event rates at the projected end of the study, i.e. $Z_N = (p_1 - p_2 - \delta) / \sqrt{2\bar{p}(1-\bar{p})/N}$, $\bar{p} = (p_1 + p_2)/2$, $p_i = (S_i + T_i)/N$ and $\eta = 1 - \alpha$.

7.2.4. Details of the Interim Analysis

To assess the comparability of the two groups, summary statistics of the baseline characteristics for the available patients within the analysis set will be presented to iDMC by treatment groups; formal statistical tests will not be performed.

Subject disposition, will also be summarized by treatment groups, number and percentages of the following will be presented:

1. subjects who were screened but not subsequently randomized;

2. subjects who were randomized;
3. subjects who were randomized and have completed the randomized treatment period;
4. subjects who were randomized and prematurely discontinued from the study before completion of the randomized treatment period;
5. subjects who had PSA reduction of 50% or more but missed the confirmation visit;
6. subjects included in the FAS.

The number and percentage of subjects listed above will be based on all subjects enrolled.

Demographics (e.g., gender, age, race, etc.) and baseline characteristics (e.g., stratification factors, and the results from PSA assessments) will be summarized using descriptive statistics by randomized treatment group. These summaries, with the exception of the PSA data, are included in the routine safety data resented to the iDMC at their scheduled meetings. Continuous data will be described using descriptive statistics: n, mean, standard deviation (SD), median (if $n \geq 2$), minimum and maximum. Categorical data will be summarized in contingency tables with frequencies and appropriate percentages in each category. When the frequency is zero, the percent will be suppressed in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in the count tabulations where necessary to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in the randomized group within the FAS analysis set.

The predictive power of reaching the primary efficacy endpoint will be evaluated on the FAS analysis set; the result will be presented to the iDMC along with the frequency and proportion of subjects with confirmed ≥ 50% reduction in PSA response for each treatment group.

Following the decision rules described in Section 7.2, the iDMC will review the results and will provide the Sponsor's management with a recommendation regarding the continuation or stopping of the study.

If the study is determined to be terminated by the Sponsor, complete statistical analyses of all study endpoints will be performed as detailed in Section 8.

8. FINAL ANALYSES

When the last randomized subject completes the randomized treatment period, or the study is determined to be terminated after the interim analysis, complete statistical analyses of all study endpoints will be performed. This analysis will be considered final; a formal study report will be produced based on the analyses and the study conclusions will be based on the results from these analyses.

When the last randomized subject completes the long-term survival follow-up visit or has discontinued from long-term follow-up, overall survival and a summary of adverse events of special interest will be updated in a long-term safety update study report, but the efficacy endpoints will not be re-analyzed.

8.1. Significance Level

In general, inferential statistical tests will be two-sided and will be performed at alpha levels of 0.05, unless otherwise noted.

8.2. Analysis Populations

Subjects who give informed written consent but are not dispensed study medication are considered screen failures.

8.2.1. PSMA Imaged Population

The PSMA Dosed set is defined as all subjects who received any dose of ^{18}F-DCFPyL. This population will be used to summarize AEs that occurred following dosing with ^{18}F-DCFPyL.

8.2.2. Safety Population

The safety set is defined as all subjects who received any dose of study drug defined as I-131-1095 and/or enzalutamide. All enrolled subjects will be assumed to have taken the study treatment unless otherwise confirmed. If it is confirmed that a subject never took a dose of the study treatment, then the subject will be excluded from all safety analysis. Any subject who received any amount of I-131-1095 will be assigned to the I-131-1095 treatment group. All subjects in the safety population will be analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, if there is a discrepancy.

The safety set will be used for the safety and baseline parameters.

8.2.3. Full Analysis Set (FAS) Population

The FAS is defined as all randomized subjects and will be analysed 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.

The FAS follows the ITT principles defined in ICH-E9[1] and is defined as all randomized subjects and will be analyzed according to the randomization schedule. 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.

8.2.4. Per-Protocol (PP) Population

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 subjects who did not complete at least one post-baseline PSA assessment. The PP analysis of the primary endpoint will be used as one of the sensitivity analyses.

The PP Set will consist of the Safety Set excluding subjects with major protocol violations or who did not complete at least one post-baseline PSA assessment. The PP analysis of the primary endpoint will be used as one of the sensitivity analyses.

8.3. Baseline Definition

The last value of any observation prior to the administration of the first dose of the study treatment will be used as the baseline value.

Baseline is defined as the last non-missing result prior to administration of I-131-1095 or Enzalutamide.

8.4. Derived Data

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

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

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

8.4.1. Visits and Visit Windows

In the analysis of each study endpoint, all study visits with the endpoint measurement will be arranged in the ascending order chronologically by subject, including both scheduled and unscheduled study visits as long as the visits occur within the randomized treatment period.

However, for subjects with missing confirmed primary endpoint responses (i.e.: PSA reduction of ≥50%), data obtained at unscheduled visits will be considered:

1. If the outcome (i.e., PSA values) is not available at the scheduled visit or the scheduled visit was not performed, but there is at least one unscheduled visit that occurred within the visit window of the scheduled visit, the missing outcome value(s) from the scheduled visit(s) will be replaced with the one from the closest unscheduled visit that occurred within the scheduled visit window; if two unscheduled visits occurred within the same distance from the target date of the scheduled visit, the outcome measurement from the latter visit will be used to replace the missing outcome at the scheduled visit.
2. If there are still some missing values:
   - for the primary efficacy endpoint: the missing PSA value at the scheduled visit will be handled following the details in Section 8.5.1.
   - for other efficacy endpoints, missing outcome values will not be imputed; only observed values will be included in the analysis of the endpoint.

For subjects who do not have a confirmed PSA reduction of ≥50%, only missing PSA values at scheduled visits will be handled as follows:

- if there is at least one unscheduled PSA measurement in a visit window for the scheduled visit, the PSA value from the unscheduled visit will be used as the PSA value at the scheduled visit; if there are two or more unscheduled PSA measurements, the one from the closest visit will be used (in case the unscheduled visit occurs at the same distance from the target visit of the scheduled visit, the unscheduled PSA measurement from the latter visit will be used).
- if there are still missing PSA values at the scheduled visit, the missing PSA value at the scheduled visit will be handled as detailed in Section 8.5.1.

The lower bound of the first scheduled endpoint visit is Day 1 and the upper bound of the last scheduled endpoint visit within the randomized treatment period is the end of the randomized treatment period, which is approximately 365 days following the first dose of study drugs.

Otherwise, the lower bound of a Visit Window is the

$$\lfloor(\text{the target day of the current scheduled visit} + \text{the target day of the previous scheduled visit})/2\rfloor;$$

the upper bound of a visit window is the

$$\lfloor(\text{the target day of the current scheduled visit} + \text{the target day of the previous scheduled visit})/2\rfloor + 1;$$

In summary, the visit window for PSA outcomes is described in Table 3.

Table 3: Visit Windows for PSA Outcomes

Study Week	**5**	**9**	**13**	**17**	**21**	**25**	**28**	**36**	**42**	**47**
Target Day from First Dose	36	64	92	120	148	176	197	253	295	330
Lower Bound visit Window	1	51	79	107	135	163	187	225	275	313
Upper Bound Visit Window	50	78	106	134	162	186	225	274	312	365

Data collected within each visit window for a visit will be presented for that visit in the summary tables. Unscheduled visits will only be presented in the listing. For variables or analyses that involve responses over time, such as PSA, all data will be used for this.

8.5. Handling of Missing Data

8.5.1. Missing Primary Efficacy Endpoints

For subjects without confirmed responses (the confirmed PSA reduction of ≥ 50% for primary efficacy analysis), missing PSA levels as originally collected at each scheduled visit will be handled in two steps:

1. Replacing the missing outcome values at the scheduled visit with the outcome values from an unscheduled visit that occurred within the visit window of the scheduled visit following the approach as described in Section 8.4.1;
2. If however, there are still some missing values, then the missing values at the scheduled visit will be imputed together with the outcome values from all scheduled visits for all subjects in the analysis population, including subjects with confirmed responses and subjects without confirmed responses and including the replaced outcome values at the scheduled visit after step 1, but excluding the unscheduled visits.

The following three different approaches may be used:

i. Multiple imputation (MI) assuming missing at random (MAR) for all missing values within the same randomization group; the covariates of the imputation model include age, enrollment stratum (intermediate risk or high risk) and baseline PSA. The imputation will be carried out in the following steps:

   a. If any of the baseline covariates is missing, the first step is to impute the missing baseline covariates using Monte-Carlo Markov Chain (MCMC) approach to produce 100 imputed datasets using the following sample code:

```
/* Impute missing baseline covariates 100 times */

PROC MI data=indata0 nimpute = 100 round=.1 minimum=0 maximum=100
seed=&seed0 out=imp0;
  MCMC;
  VAR age stratum psa0;
run;
```

   b. If the first missing PSA values are observed at week X, then impute the missing post baseline PSA values ν times for week *X* using all the baseline covariates from the above model + the post baseline PSA values at the visit prior to week *X*. Missing values will be imputed within each treatment group within each imputed dataset.

      For example: if the first missing PSA value are observed at week 13, then the imputation model will include all the baseline covariates, the PSA values obtained from week 5, and the PSA values collected at week 9.

```
/* Impute post-baseline PSA levels at week13 */

PROC MI DATA= imp0 NIMPUTE=ν SEED=&seed1 OUT=imp1;

BY _Imputation_ treat;

CLASS treat stratum;

VAR age stratum psa0 psa5 psa9 psa13;

MONOTONE regression (psa13=age stratum psa0 psa5 psa9);

RUN;
```

Then impute the missing PSA values for the next visit (one visit at a time) until all the missing post-baseline PSA values were imputed.

```
/* Impute the missing PSA values sequentially until all missing PSA values are imputed */
PROC MI DATA= imp_xx NIMPUTE=1 SEED=&seed1 OUT=imp_yy;
BY _Imputation_ treat;
CLASS treat stratum;
VAR age stratum psa0 psa5 psa9 psa13 psa17 psa21 psa25 psa28 psa36 psa42 psa47;
MONOTONE regression (psa47=age stratum psa0 psa5 psa9 psa13 psa17 psa21 psa25 psa28 psa36 psa42);
RUN;
```

If none of the baseline covariates are missing, then the first step is to impute the missing PSA values at the 1st post baseline visits, where ν=100; otherwise, ν=1; then impute the missing PSA values at the 2nd visit using the previously imputed dataset, then the 3rd, … until all missing PSA values were imputed.

After all missing PSA values were imputed, the confirmed PSA reduction of ≥ 50% will be 1, otherwise it will be 0; the confirmation must be at least 3 weeks following the reduction.

ii. Pattern mixture model assuming missing-jump-to-control: missing PSA values due to missing visits or unable to perform measurement will be imputed using MI assuming missing at random; while missing values because of early drop out due to AEs or lack of efficacy will be imputed using control-based imputation: the missing values from subjects randomized to enzalutamide plus I-131-1095 will be imputed together with all the observed and missing values from the subjects in the enzalutamide group.

For subjects without confirmed responses (the confirmed PSA reduction of ≥ 50% for primary efficacy analysis), those with missing PSA values at the scheduled visit after step 1 will be kept into two mutually exclusive groups:

a. Subjects with missing PSA values due to missing visits or unable to perform measurement

The subjects will be grouped together with

- those with confirmed responses,
- those without confirmed responses, but PSA values are available at all scheduled visits after step 1

PSA values from the above subjects will be combined for imputing missing values using MI assuming missing at random. The missing PSA values will be imputed following approach 2.i.

b. Subjects with missing PSA values because of early dropout due to AEs or lack of efficacy from both the enzalutamide plus I-131-1095 and enzalutamide groups

The subjects will be grouped together with those subjects from the enzalutamide group who

- have confirmed responses,
- do not have confirmed responses, but PSA values are available at all scheduled visits after step 1 (Section 8.5.1)

PSA values will be combined together with imputed missing values using MI. The missing PSA values will be imputed following steps 2.i.a and 2.i.b (Section 8.5.1).

iii. A tipping point analysis will be performed for the binary efficacy endpoint if the result from the main analysis (using observed data) of the endpoint is significant. The tipping point analysis will be carried out at the subject level for subjects with missing responses:

a. each missing response in the enzalutamide group will be replaced with a confirmed response one at a time, followed with the planned analysis (Cochran-Mantel-Haenszel [CMH] test) until the analysis results turn from significant to non-significant.

b. if the analysis result does not change even after all missing responses in the enzalutamide group are replaced with confirmed responses, then the subjects with missing response in the enzalutamide plus I-131-1095 group will be assumed to have no confirmed response one at a time, followed with the planned analysis (Cochran-Mantel-Haenszel [CMH] test) until the analysis results turn from significant to non-significant.

8.5.2. Missing Secondary or Exploratory Endpoints

If endpoint assessments are reported at unscheduled visits within the visit window for an endpoint, that assessment will be used in the calculation of the endpoint. Otherwise, formal statistical models will not be implemented to impute the missing secondary or exploratory endpoints and the endpoints will be calculated using the observed data.

For subjects who have no confirmed PSA measurements post baseline, multiple imputations will be applied to impute the binary outcome of a 50% confirmed reduction in PSA from randomization. It is assumed that these data are missing at random (MAR)[7] where the probability of the outcome being missing depends only on observed measurements. There is also an assumption that the data are monotone missing so data points should exist up to the time point of when the outcome is missing and not after that.

1. The first step is to implement the multiple imputation procedure, Proc MI, in SAS. There will be five multiple imputed datasets created from this procedure:

```
Proc MI out=Impute Seed=739114;
Class TRTgroup Surgery Gleason TNM_N TNM_M TNM_T ADT Radiation
PrPCTx PrNPCtx Primary;
```

```
Monotone Logistic (primary= TRTgroup Age Baseline_PSA Surgery Gleason
    TNM_N TNM_M TNM_T ADT Radiation PrPCTx PrNPCtx/Details);
Var TRTgroup Age Baseline_PSA Surgery Gleason TNM_N TNM_M TNM_T
    ADT Radiation PrPCTx PrNPCtx/Details;
Run;
```

The following baseline characteristics will be used to impute the missing primary endpoint values: Treatment group received, Age at consent, Baseline PSA, clinically relevant medical histories or surgeries (yes/no), total Gleason score at prostate cancer pathologic diagnosis, TNM Nodal stage at diagnosis,TNM metastatic stage at diagnosis, TNM primary tumor stage at diagnosis, Received perioperative ADT (yes/no), Prior cancer related radiation therapy (yes/no), Prior systemic anticancer therapy for prostate cancer (yes/no), and Prior anticancer therapy for non-prostate cancer (yes/no).

2). For each of the five iterations of the imputation generated from the MI procedure above, a chi-square test will be performed for treatment groups by primary endpoint. This will output a chi-square value with an associated degrees of freedom and probabilities. Invoke the SAS macro, COMBCHI[8], in Proc IML to combine chi-square results.

8.5.3. Missing Dates

In general, if a date value is missing, the following rules will be applied: the15th of the month will be substituted for missing day of the month, July will be substituted for missing month, and July 1 will be substituted for missing day and month, unless the imputed date is prior to the first dosing date. Then the imputed date would be the first dosing date.

8.6. Statistical Software

SAS® Software (Cary, NC) version 9.4 will be used for all analyses.

9. STATISTICAL ANALYSIS AND DATA CONVENTIONS

9.1. Data Presentation Conventions

9.1.1. General Summary Tables and Descriptive Statistics

Adverse event and medical history verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE) Global B3 September 2019.

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

Summary tables for demographics and baseline characteristics, medical history, exposure, concomitant medications, and safety endpoints will include the following columns: Enzalutamide, 1095+Enzalutamide, overall. Efficacy tables will be produced by randomized treatment groups.

9.1.2. Summary Statistics

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

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

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

9.2. Statistical Considerations

- For continuous endpoints, normality assumptions will be tested using the Shapiro-Wilk test;

  If the normality assumption was not rejected, a two-sample t-test will be generally used to compare treatment groups if there is no need to adjust for any covariates; linear mixed effect models will be used if more than one covariate needs to be included in the analysis model.

  If normality was rejected, Wilcoxon sign rank tests will be used; if covariates are needed, covariate-adjusted nonparametric tests will be used.

- For categorical endpoints, chi-square tests will be generally used to compare treatment groups (CMH will be used to adjust for stratification factors); if additional

covariates need to be addressed, generalized linear mixed effect models will be used. For chi-square tests, if the expected cell count is less than 5, Fisher's exact tests will be used instead.

- For survival and time-to-event endpoints, Kaplan-Meier plots will be produced for each treatment group separately. Stratified log-rank tests will be used to compare the treatment groups accounting for risk grouping; if however, covariates need to be adjusted, the proportional hazards assumption will be tested first using a proportionality test.

  If the proportional hazards assumption is not rejected for all covariates, a proportional hazard model will be used with adjustment of all covariates;

  If the proportional hazards assumption is rejected for one of the covariates, the covariates will be transformed by adding a timing factors as the following example, where pca is the stratification factor (PCa risk class):

```
proc phreg data=rpfs;
  model time*censor(0) = treat rpfs pca pcat;
  treatt = treat*log(time);
  pcat = pca*log(time);
  proportionality_test: test treat treatt, pcat;
run;
```

9.3. Subgroup Analyses

All subgroup analyses will be performed based on observed data (missing data will not be imputed).

The primary efficacy endpoint, rPFS and OS will be analyzed within different strata (PCa risk class). The endpoints will also be analyzed based on age (<65, 65 to <75 and 75+ years), based on race (White, Black, Other) and ethnicity (Not Hispanic or Latino, Hispanic or Latino). A subgroup analysis will examine the endpoints by randomized treatment group by baseline lactate dehydrogenase (LDH) (≤ upper limit of normal (ULN), > ULN).

If any imbalances are seen in the baseline characteristics, they will be added to a logistic regression model along with treatment.

9.4. Multiple Comparisons and Multiplicity

Adjustment for multiplicity will not be performed for secondary and exploratory endpoints. Data will be analyzed at two time points. The first will be after the randomized treatment period at one year and will include all safety and efficacy outcomes. The other will be at the end of the study and will contain only long-term AEs of special interest, concomitant medication use and survival status. Concomitant mediations taken while on randomized treatment will be defined by excluding the pre-treatment medications. The rules for defining these pre-treatment medications are as follows:

- If Concomitant medication date < randomized treatment date
- If concomitant medication year is < randomized treatment year
- If concomitant medication year = randomized treatment year and concomitant medication month < randomized treatment month

The following information will be presented for disposition:

- Number screened
- Screen failures and reasons why
- All patient population sets
- Stratification factors
- Number not randomized and who did not meet PSMA-avidity in PSMA Imaged Set
- Discontinuation after treatment but prior to randomization and reasons why
- Discontinuation after randomization and reasons why
- Number who received treatment and did not receive treatment post randomization
- Number who completed the randomization treatment period
- Number who entered the long-term follow-up period
- Number who completed the long-term follow-up period
- Discontinuation from long-term follow-up period and reasons why

The N and percentage will be presented for the Safety Set and all summaries that occur within this set. All summaries that occur prior to receiving one of the randomized treatments will just show the number of patients in each group.

9.5. Subject Disposition

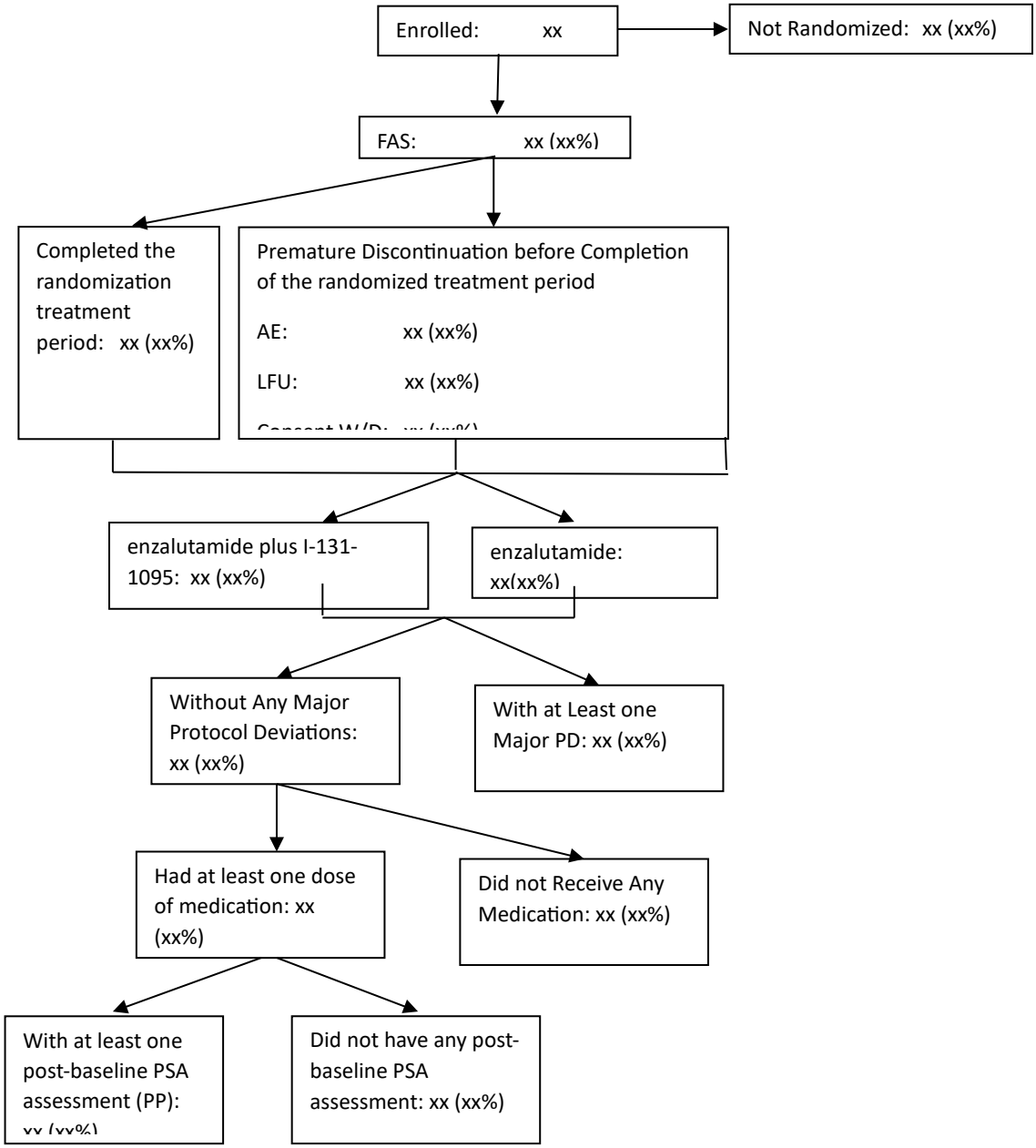
Subject disposition, will be summarized by randomized treatment group where applicable, presenting the number and percentages of the following:

- subjects who were screened but not subsequently randomized;
- subjects who were randomized;
- subjects included in the FAS;
- subjects who were randomized and have completed the randomized treatment period as noted in the end of randomized treatment CRF page;
- subjects who were randomized and prematurely discontinued from the study before completion of the randomization treatment period;

The number and percentage of subjects listed above will be based on all subjects enrolled.

In addition, a flow chart of subject disposition will also be displayed.

Figure 1: Subject Disposition Flow Chart



Abbreviations:

AE = adverse event, LFU = Lost to Follow-up, WD = withdraw

9.6. Baseline Characteristics

Baseline parameters will be summarized by treatment group; formal statistical tests will not be performed to compare the difference between the treatment groups.

9.6.1. Protocol Deviations

Protocol deviations will be listed by treatment group and overall for the type of deviation and indicated whether or not each was major. This will be displayed for the safety population.

9.6.2. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS, per-protocol and safety populations. Age at time of informed consent, age groups (<65, 65 to <75 and 75+ years), sex, ethnicity, race, height, weight and BMI will be summarized by treatment group and for all treated subjects combined. Continuous outcomes will be presented showing the N, mean, median, SD, minimum and maximum values. Discrete outcomes will show the N and percentage for each level of the result.

9.6.3. Listing of Subject Inclusion and Exclusion Criteria

Listings will be generated to show which subjects did not meet inclusion or exclusion criteria as well as any protocol deviations. These will be displayed for the safety set.

9.6.4. Prior History

9.6.4.1. Medical History, Surgical History and Prior Prostate Cancer History

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

Prior prostate cancer history will also be summarized using summary statistics for months since most recent prostate cancer pathological diagnosis, months since pathologic confirmed metastatic disease, months since last procedure/surgery for prostate cancer, baseline PSA (ng/mL) and testosterone (ng/dL). Frequencies and percentages will be presented for prior procedure/surgeries for prostate cancer, prior androgen deprivation therapy (ADT), total Gleason grade at diagnosis, primary tumor stage (T), regional lymph node stage (N), and distant metastasis stage (M).

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

9.6.4.2. Cancer-Related Radiation History

Prior cancer-related radiation history will also be summarized using summary statistics for months since most recent radiation, duration of most recent radiation, and dose (Gy) of most recent radiation. If dose is captured in units of centigray (cGy) then divide by 100 to convert to Gy. If dose is captured in units of frequencies and percentages, then prior radiation will be presented as site of radiation, regimen, regimen type and whether perioperative ADT was administered with radiation.

Cancer-related radiation history will be presented for the safety set, the FAS and the per-protocol set.

9.6.4.3. Prior Medication History

Prior medications will be summarized by ATC4 class and generic name using frequencies and percentages. Prior medications will also be listed. Verbatim terms will be coded using the WHO DDE. All medications with start date prior to or following the first dose of any study medication and continuing in the randomized treatment period are considered concomitant medications.

Prior medication history will be presented for the safety set, and the FAS.

9.6.4.4. Prior Anticancer Therapy

Prior anticancer treatments will be summarized by ATC4 class and generic name using frequencies and percentages. Prior medications will also be listed. Verbatim terms will be coded using the WHO DDE. Section 6.8.2 describes how prior medications will be determined.

Prior anticancer therapy will be presented for the safety set, the FAS and the per protocol set.

Prior systemic anticancer therapies for prostate cancer are captured by regimen and each patient can have multiple treatment regimens.

Prior prostate cancer systemic therapies will be summarized for months from last systemic therapy stop date to dose 1, Months since last disease progression by any definition (by rising PSA, by radiographic progression, and by clinical progression).

All prior cancer treatments will be generated for the FAS, the safety set and the per-protocol set.

9.7. Analysis of the Efficacy Endpoints

All analyses performed on the primary endpoint will be performed for the FAS, and the per-protocol (PP) populations.

9.7.1. Analysis of the Primary Efficacy Endpoint

9.7.1.1. Main Analysis of the Primary Efficacy Endpoint

The main analysis of the primary endpoint is the comparison of the proportion of subjects who have at least a 50% reduction from Baseline in PSA confirmed at least 3 weeks later; a CMH test with adjustment for stratification factor (PCa risk factor) will be carried out using complete cases for the FAS population (missing data will not be imputed for this analysis). The p-values from the “Row Mean Score Differ”, the CMH-adjusted odds ratio and relative risk and the corresponding 95% CIs will be presented.

```
PROC FREQ DATA= PSA_reduction_data;

TABLES stratification_factors *treat*PSAresponder / CHISQ CMH(BDT);

RUN;
```

Within each stratum, the number and proportion of patients with confirmed PSA reduction of ≥ 50% for each of the groups, the difference in proportions between the groups along with the 95% Santner-Snell exact confidence interval (CI) of the differences will be presented.

```
PROC FREQ DATA=PSA_reduction_data;

BY stratification_factors;

TABLES treat* PSAresponder /RISKDIFF(CL=(EXACT));

EXACT RISKDIFF;

RUN;
```

9.7.1.2. Sensitivity Analyses of the Primary Efficacy Endpoint

Except for the first sensitivity analysis on the PP population, the rest of sensitivity analyses will be performed on the FAS.

1. The CMH test will be performed based on complete cases (missing values will not be imputed) for the PP population.

The following sensitivity analyses (1, 2 and 3) will be performed on the FAS; missing values will not be imputed.

1. Chi-square tests will be performed based on complete cases (missing values will not be imputed) without adjusting for stratification factors for FAS;
2. The first occurrence of 50% reduction in PSA without any confirmation;
3. The first occurrence of 50% reduction in PSA confirmed any time after the first occurrence FAS population will be used and missing values will not be imputed.

The following sensitivity analyses (1, 1 and 2) will be carried out to evaluate the impact of the missing data to the analysis result; these 3 sensitivity analyses will be performed for FAS.

1. Tipping point analysis (see Section 8.5.1, step 2, option iii for details)

The following sensitivity analyses will be performed following the details in Section 8.5.1. The CMH test will be performed accordingly.

1. MI assuming missing-at-random (MAR)
2. Pattern mixture model assuming missing-jump-to-control

For 1 and 2, the common odds ratio and the corresponding 95% CIs can be obtained through the following SAS code; the common relative risk and corresponding 95% CIs can be obtained similarly (with some slight change to the SAS code).

```
*** Obtain Mantel-Haenszel estimate of the common odds ratio adjusted for

baseline score category ***;


PROC FREQ DATA=datain_mi;
```

```
TABLES stratification_factors*treat*PSAreduction / CMH;
ODS OUTPUT COMMONRELRISKS=comrrout;
BY _Imputation_;
RUN;

*** Log-transform odds ratio estimates
and obtain standard error from confidence intervals ***;

DATA ormh_t; SET comrrout(WHERE=(StudyType="Case-Control"));
log_or_mh_value=log(VALUE);
log_or_mh_se=(log(UPPERCL)-log(LOWERCL))/(2*1.96);
RUN;

PROC MIANALYZE DATA= ormh_t;
ODS OUTPUT PARAMETERESTIMATES=mian_lgsodds_t;
MODELEFFECTS log_or_mh_value;
STDERR log_or_mh_se;
RUN;

*** Back-transform combined values;

DATA mian_lgsodds_bt; SET mian_lgsodds_t;
Estimate_back = EXP(ESTIMATE); *Pooled odds ratio;
LCL_back=Estimate_back*EXP(-1.96*STDERR); *Pooled lower limit;
UCL_back=Estimate_back*EXP(+1.96*STDERR); *Pooled upper limit;
RUN;
```

9.7.2. Analysis of the Secondary Efficacy Endpoints

All secondary endpoints will be analyzed using the FAS.

The endpoint of ORR will test for differences in proportions between treatment groups using a chi-squared test. If any of the expected cell frequencies is less than 5, then a 2-sided Fisher's exact test will be used. The number and proportion of patients with this endpoint will be presented for each treatment group along with the difference in proportions, the p-value for this difference based on the above test and a 95% confidence interval of the differences in proportions. The Wald asymptotic confidence interval will be presented if the Chi-square statistic was performed and an Exact Clopper-Pearson confidence interval will be presented if the Fisher's exact test was used.

The following secondary endpoints will compare the survival functions of these time-to-event variables between treatment groups using a stratified log-rank test. Subjects will be censored at the date of the occurrence of withdrawal or study completion, whichever occurs the first. For each treatment group, the number of subjects, number and percentage of patients with events, number and percentage censored, median time to event with 95% CI, and the probability of event free at 1-year from the first dose of treatment and the corresponding 95% CI will be presented. The p-value from the log-rank test will also be presented. Kaplan-Meier plots will be presented.

- OS defined as time from randomization to death
- PSA progression defined as time from randomization to date of first confirmed PSA progression value defined in section 4.2.2
- 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

To test the assumptions of proportional hazards, a proportionality test as described in section 9.2 will be used. If the assumptions are not violated, then proportional hazards models using additional covariates may be performed as exploratory analyses.

9.7.3. Analysis of the Exploratory Efficacy Endpoints

Exploratory endpoints will be analyzed for the FAS.

The proportion of subjects with pain progression defined from the BPI-SF pain intensity score in Section 6.7.5 as ≥30% increase from Baseline to 6 months will be analyzed using a chi-squared test to compare the 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.

Normality of the following 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 effects at the visits where the data were collected; otherwise, a generalized model will be used.

- ^{18}F-DCFPyL uptake defined by SUVmax
- Number of ^{18}F-DCFPyL positive lesions

- Overall score from FACT-P
- Physical domain from FACT-P
- Social/family domain from FACT-P
- Emotional domain from FACT-P
- Functional well-being domain from FACT-P
- Prostate cancer scale from FACT-P
- SF-12v2 PCS score
- SF-12v2 MCS score
- aBSI scores
- ECOG performance status
- The following BPI parameters: Worst Pain, Least Pain,

  Average Pain, Pain now, Pain Intensity and Interference.

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 by treatment group.

9.7.4. Derivations for BPI-SF, FACT-P and SF-12

- Brief Pain Inventory- Short Form (BPI-SF)

  Questions 3-6 representing worst pain, least pain, average pain and pain now will each be summarized separately. They should each have numeric values ranging from 0 representing no pain to 10 representing pain as bad as you can imagine. A composite score for Pain Intensity will also be derived by taking the mean of these questions.

  Question 9A-G represent relations with others, enjoyment of life, mood, sleep, walking, general activity and working. Each of these questions should have numeric results of 0 representing no interference to 10 complete interference. A composite score for Interference will be derived by taking the average of these questions. This composite score will only be created if at least 4 of these 7 questions are non-missing.

- The following composite scores will be derived from the questions on the FACT-P questionnaire:
  - Physical Well-Being (PWB) = questions 1-7 representing lack of energy, nausea, trouble meeting the needs of the family, pain, side effects of treatment, feeling ill, and forced to spend time in bed. Each of these questions should be numeric ranging from 0 (not at all) to 4 (very much). First, reverse scoring for each question within subject by subtracting each response from 4. PWB Score = sum of these questions after reserve scoring.

- PWB subscale = (PWB Score x 7)/number of non-missing questions in this subscale. This will only be calculated if at least 4/7 questions are non-missing).
- Social/Family Well-Being (SWB) = 7 questions representing close to friends, emotional support from family, support from friends, family accepted illness, family communication about illness, close to partner and satisfaction with sex life. Each of these questions should be numeric ranging from 0 (not at all) to 4 (very much). If Not Applicable is checked then set to missing.
- SWB Score = sum of these questions.
- SWB subscale = (SWB Score x 7)/number of non-missing questions in this subscale. This will only be calculated if at least 4/7 questions are non-missing).
- Emotional Well Being (EWB) = 6 questions representing feeling sad, satisfaction with coping with illness, losing hope in fight against illness, feeling nervous, worrying about dying, and worrying condition will get worse. Each of these questions should be numeric ranging from 0 (not at all) to 4 (very much). Reverse the scoring for all questions except about satisfaction with coping with illness by subtracting responses from 4.
- EWB Score = sum of these questions after reverse scoring.
- EWB subscale = (EWB Score x 6)/number of non-missing questions in this subscale. This will only be calculated if at least 3/6 questions are non-missing).
- Functional Well Being (FWB) = 7 questions representing ability to work, work is fulfilling, able to enjoy life, accepted illness, sleeping well, enjoying things done for fun, and quality of life now. Each of these questions should be numeric ranging from 0 (not at all) to 4 (very much).
- FWB Score = sum of these questions.
- FWB subscale = (FWB score x 7)/number of non-missing questions in this subscale. This will only be calculated if at least 4/7 questions are non-missing).
- Prostate Cancer Subscale (PCS) = 12 questions listed under Additional Concerns that represent losing weight, a good appetite, aches and pains that bother me, parts of body where I experience pain, pain keeping me from doing things I want to do, satisfied with present comfort level, able to feel like a man, trouble moving bowels, difficult urinating, urinate more frequently than usual, urinating limits my activities, and maintain an erection. All questions will be reversed by subtracting their responses from 4 except for 4 questions: a good appetite, satisfied with present comfort level, ability to feel like a man, and maintain an erection.
- PCS Score = sum of these questions after reverse scoring.
- PC subscale = (PCS Score x 12)/number of non-missing questions in this subscale. This will only be calculated if at least 6/12 questions are non-missing).
- Trial Outcome Index (TOI) = PWB Score + FWB Score + PC Score.

- Total Score = PWB Score + SWB Score + EWB Score + FWB Score + PCS Score. This will only be calculated if at least 22/27 of the questions used to derive this are non-missing and each of the subscale scores are not missing.

There is a SAS program that comes with the user manual and will be used to validate the results generated from the above instructions.

- SF-12v2 Health Survey

The SF-12v is comprised of the following domains.

Domains: Question/s within Domain

- Physical Function (PF): questions 2a and 2b
- Role-Physical (RP): questions 3a and 3b
- Bodily Pain (BP): question 5
- General Health (GH): question 1
- Vitality (VT): question 6b
- Social Functioning (SF): question 7
- Role-Emotional (RE): questions 4a and 4b
- Mental Health (MH): questions 6a and 6c

Scoring should be completed by applying the following steps in order:

1. The scoring must be reversed for the following domains by subtracting each result from 6: BH, GH, VT and question 6a from MH.
2. Missing values for the domains with 2 questions will be imputed using the MSE algorithm.
3. Generate the domains by summing the questions within each.
4. Transform all domains to 0-100 scale using the following formula:

   [(Actual score – Lowest score)/difference in range of possible scores] x 100
5. Compute Z-score for each transformed domain = (Domain score – population mean)/population.
6. Transform Z-score to T-scores = 50 + (Domain Z score x 10).
7. Aggregate Component Scales (MCS and PCS) = ∑ (Domain Zscore x factor score).
8. MCS and PCS T score = 50 + (Aggregate Component Scale x 10).

9.8. Safety and Tolerability Data

9.8.1. Adverse Events - Preferred Term and System Organ Class Summaries

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. These AEs will therefore not be summarized in the overall AE tables, but separately.

During the treatment period, AEs/SAEs collection will begin after the first administration of I-131-1095 or enzalutamide and will continue until the end of the Treatment Period.

After the treatment period through the end of the survival follow-up period, the only AEs that will be collected are adverse events of special interest (AESI) as listed in the study protocol. An AESI is an event of scientific and medical concern specific to I-131-1095. Therefore, the causal assessment assigned to I-131-1095 must be "related" or "possibly related"; if the causal assessment is "not related" or "unlikely related" to I-131-1095, it will not be considered an AESI.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1.

9.8.1.1. Summaries of Adverse Event Incidence

A high-level summary of TEAEs will be presented for subjects who had at least one TEAE overall, seriousness, and leading to discontinuation of treatment. Since the cumulative number of cycles with I-131-1095 may differ among subjects, these summaries will also be presented by cycle when the adverse event start date is reported:

Cycle	I-131-1095	Enzalutamide
1	At least 1 dose and AEs collected up to the first occurrence of the 2nd dose or Day 56	At least 1 dose and AEs collected up to Day 56
2	At least 2 doses of drug, and AEs collected up to the first occurrence of the 3rd dose or 56 Days from dose 2.	At least 1 dose after Day 56 and AEs collected up to Day 112
3	At least 3 doses of drug, and AEs collected up to the first occurrence of the 4th dose or 56 Days from dose 3.	At least 1 dose after Day 112 and AEs collected up to Day 168
4	At least 4 doses of drug	At least 1 dose of drug taken after Day 168

Treatment-emergent adverse events will be summarized by SOC and PT using the frequency and percentage of subjects experiencing any adverse event, experiencing each SOC and experiencing

each PT within each SOC, using the safety set. The number of occurrences of each adverse event will be included.

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

Treatment-emergent adverse events will be summarized by relationship to study drug. The most closely related occurrence of each event will be summarized by SOC and PT using the frequency and percentage of subjects experiencing any adverse event, experiencing each SOC and experiencing each PT within each SOC by treatment group and overall, using the safety analysis set. Since relationship is captured for ^{18}F-DCFPyL, I-131-1095 and Enzalutamide separately, the data will be presented for patients treated with Enzalutamide only and for the patients treated with at least one dose of 1095, their related AEs will be summarized showing events that were related to Enzalutamide separately from the events related to I-131-1095.

If any adverse events are reported as related to ^{18}F-DCFPyL, a summary of the incidence of the adverse events will be presented by SOC and MedDRA preferred term. All adverse events related to ^{18}F-DCFPyL will be included in patient listings.

9.8.1.2. Missing and Partial AE Onset Dates

Missing and partial AE onset date will be handled as detailed in Section 8.5.3.

AEs that occur within 24 hours of ^{18}F-DCFPyL administration will be summarized for all patients while on ^{18}F-DCFPyL. Treatment emergent AEs are captured on or after study drug treatment (^{18}F-DCFPyL, I-131-1095 or Enzalutamide).

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

An overall summary table will be generated including the incidences of serious adverse events (SAEs), adverse events of special interest (see protocol Section 12.1.1), adverse events that led to discontinuation from the study and deaths by SOC and preferred term within SOC.

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

9.8.2. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

Exposure to study drug will be summarized using summary statistics for cumulative dose received, treatment duration, total number of doses administered, at least 1 dose administered, at least 1 dose reduction due to dosimetry, dose-limiting toxicities (DLTs). The summaries will be presented by actual treatment received and overall for the safety set. A summary of I-131-1095 dose delays and reductions will be presented by reason(s) for the delays and reductions.

9.8.3. Concomitant and Other Medications

Medications will be coded using the World Health Organization Drug Dictionary (WHODDE) Version 23.1. Concomitant medications are defined as medications taken on or after treatment with I-131-1095 or Enzalutamide. These will be summarized by ATC4 class and generic term using frequencies and percentages by treatment group and overall for the safety analysis set.

9.8.4. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Section 8.5.3 defines how pre-treatment medications will be defined when medications dates are incomplete. If these do not qualify for this definition, then they will be considered concomitant medications.

9.8.5. Laboratory Data

Clinical chemistry, hematology and urinalysis data and changes from baseline values will be summarized by study visit using descriptive statistics. Shift tables will be prepared tabulating the last reported status (high, low, normal) for each analyte against the respective baseline status.

For laboratory results, baseline is defined as the last assessment just prior to the first dose of 1095 or Enzalutamide (Day 1), regardless of whether it was scheduled, retest, or unscheduled. Each lab parameter will be summarized along with a change from Baseline value for each visit. All lab parameters will be presented in International System of Units (SI) units.

Summary statistics for observed and change from baseline values of each laboratory parameter will be presented by visit for the safety set. Labs will include hematology and chemistry. A shift table will also be presented showing the shift in values from Baseline to follow up (below LLN, within LLN and ULN, above ULN, and missing). Listings will be prepared for all patient lab results as well as listings of abnormal lab values.

9.8.6. Vital Signs

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

9.8.7. Physical Examinations

Clinically relevant physical examination findings will be summarized with medical history data. New clinically significant findings following dosing will be summarized as adverse events.

Clinically significant abnormal physical exam findings will be captured as AEs if it qualifies or in the medical history if prior to study drug treatment.

10. REFERENCES

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2. Scher HI, Morris MJ, Stadler WM et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 2016; 34:1402-1418.
3. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.
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6. Matsubara N, Yamada Y, Tabata K, et al. Abiraterone followed by enzalutamide versus enzalutamide followed by abiraterone in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer. Clin Gentourin Cancer 2018; 16:142-148.
7. Alexei Dmitrienko and Ming-Dauh Wang. Bayesian predictive approach to interim monitoring in clinical trials. *Statistics in Medicine*, 2006; 25:2178-2195.

11. APPENDIX

11.1. Table of Contents for Data Displays

Tables

#	Title	Population	Comment
14.1.1	Summary of Subject Disposition	Enrolled	Unique
14.1.2.1	Summary of Demographic and Baseline Characteristics	Safety	Unique
14.1.2.2	Summary of Demographic and Baseline Characteristics	FAS	Repeat
14.1.2.3	Summary of Demographic and Baseline Characteristics	PP	Repeat
14.1.12	Summary of Exposure to Study Drug by Randomized Treatment Group	Safety	Unique
14.1.13	I-131-1095 Dose Delay	Safety	Unique
14.3.1.1	Summary of Adverse Events by Randomized Treatment Group	Safety	Unique
14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.3	Summary of Serious Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.4	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.5	Summary of 18F-DCFPyL-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.6	Summary of Treatment-Emergent Adverse Events of Special Interest by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.7	Summary of Treatment-Emergent Adverse Events with CTCAE Toxicity Grades of 3 and Above by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat
14.3.1.8	Summary of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Randomized Treatment Group	Safety	Repeat

14.3.1.9	Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and CTCAE Grade	Safety	Repeat
14.3.1.10	Summary of Treatment-Emergent Adverse Events Related to I-131-1095 or Enzalutamide by System Organ Class, Preferred Term, and CTCAE Grade	Safety	Repeat
14.3.5.4	Shift of Clinical Chemistry Values from Baseline to Worst Post-Baseline Observation based on CTCAE Toxicity Grade by Randomized Treatment Group	Safety	Unique
14.3.5.5	Shift of Hematology Values from Baseline to Worst Post-Baseline Value based on CTCAE Toxicity Grade by Randomized Treatment Group	Safety	Repeat
14.3.5.6	Shift of Chemistry Values from Baseline to Worst Post Baseline Value based on Normal Range by Randomized Treatment Group	Safety	Repeat
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14.3.5.1	Summary of Actual Values and Changes from Baseline in Clinical Chemistry Data by Randomized Treatment Group and Study Visits	Safety	Unique
14.3.5.2	Summary of Actual Values and Changes from Baseline in Hematology Data by Randomized Treatment Group and Study Visits	Safety	Repeat
14.3.5.3	Summary of Actual Values and Changes from Baseline in Urinalysis Data by Randomized Treatment Group and Study Visits	Safety	Repeat
14.3.6	Summary of Actual Values and Changes from Baseline in Vital Signs by Randomized Treatment Group and Study Visits	Safety	Unique
14.3.7	Summary of ECG Data and Changes from Baseline by Randomized Treatment Group, Study Visit, and Timepoint	Safety	Unique
14.1.3.1	Summary of Prostate Cancer History	Safety	Unique
14.1.3.2	Summary of Prostate Cancer History	FAS	Repeat
14.1.3.3	Summary of Prostate Cancer History	PP	Repeat
14.1.4.1	Summary of Medical and Surgical History	Safety	Unique
14.1.4.2	Summary of Medical and Surgical History	FAS	Repeat
14.1.4.3	Summary of Medical and Surgical History	PP	Repeat
14.1.5.1	Summary of Cancer-Related Radiation History	Safety	Unique

14.1.5.2	Summary of Cancer-Related Radiation History	FAS	Repeat
14.1.5.3	Summary of Cancer-Related Radiation History	PP	Repeat
14.1.6.1	Summary of Prior Medication History	Safety	Unique
14.1.6.2	Summary of Prior Medication History	FAS	Repeat
14.1.7.1	Summary of Concomitant Medications	PP	Repeat
14.1.8.1	Summary of Prior Anticancer Therapy for Non-Prostate Cancer	Safety	Unique
14.1.8.2	Summary of Prior Anticancer Therapy for Non-Prostate Cancer	FAS	Repeat
14.1.8.3	Summary of Prior Anticancer Therapy for Non-Prostate Cancer	PP	Repeat
14.1.9.1	Summaryof Prior Systemic Anticancer Therapy for Prostate Cancer	Safety	Unique
14.1.9.2	Summary of Prior Systemic Anticancer Therapy for Prostate Cancer	FAS	Repeat
14.1.9.3	Summary of Prior Systemic Anticancer Therapy for Prostate Cancer	PP	Repeat
14.1.10.1	Summary of Time Since Last Prior Systemic Anticancer Therapy for Prostate Cancer	Safety	Unique
14.1.10.2	Summary of Time Since Last Prior Systemic Anticancer Therapy for Prostate Cancer	FAS	Repeat
14.1.10.3	Summary of Time Since Last Prior Systemic Anticancer Therapy for Prostate Cancer	PP	Repeat
14.1.11.1	Summary of Concurrent Procedures	Safety	Unique
14.2.1	Primary Efficacy Endpoint, Proportion of PSA Responders by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.2.1	Proportion of PSA Responders by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.2.2	Proportion of PSA Responders by Randomized Treatment Group and Risk Stratification, Not Adjusted for Stratification Factors	PP	Repeat
14.2.2.3	Proportion of PSA Responders by Randomized Treatment Group and Risk Stratification, Response not Confirmed	FAS	Unique
14.2.2.4	Proportion of PSA Responders by Randomized Treatment Group and Risk Stratification, Any Confirmation of Response	FAS	Unique
14.2.3.1	Summary of Serum PSA (ng/dL) Responders Using Multiple Imputation Assuming Missing Not at Random	FAS	Unique
14.2.3.2	Summary of Serum PSA (ng/dL) Responders Using Multiple Imputation Assuming Missing at Random	FAS	Repeat

14.2.3.3	Summary of Serum PSA (ng/dL) Responders Using Multiple Imputation with a Pattern Mixture Model Assuming Missing-Jump-to-Control	FAS	Unique
14.2.4.1	Subgroup Analysis of PSA Responders by Randomized Treatment Group and Age	FAS	Unique
14.2.4.2	Subgroup Analysis of PSA Responders by Randomized Treatment Group and Race	FAS	Repeat
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14.2.4.4	Subgroup Analysis of PSA Responders by Randomized Treatment Group and Baseline LDH	FAS	Repeat
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14.2.8.1	Summary of Best Confirmed RECIST Response by Randomized Treatment Group	FAS	Unique
14.2.9.1	Overall Survival by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.9.2	Subgroup Analysis of Overall Survival by Randomized Treatment Group and Age	FAS	Unique
14.2.9.3	Subgroup Analysis of Overall Survival by Randomized Treatment Group and Race	FAS	Repeat
14.2.9.4	Subgroup Analysis of Overall Survival by Randomized Treatment Group and Ethnicity	FAS	Repeat
14.2.9.5	Subgroup Analysis of Overall Survival by Randomized Treatment Group and Baseline LDH	FAS	Repeat
14.2.10.1	Time to PSA Progression by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.11.1	Radiographic Progression Free Survival by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.11.2	Subgroup Analysis of Radiographic Progression Free Survival by Randomized Treatment Group and Age	FAS	Unique
14.2.11.3	Subgroup Analysis of Radiographic Progression Free Survival by Randomized Treatment Group and Race	FAS	Repeat

14.2.11.4	Subgroup Analysis of Radiographic Progression Free Survival by Randomized Treatment Group and Ethnicity	FAS	Repeat
14.2.11.5	Subgroup Analysis of Radiographic Progression Free Survival by Randomized Treatment Group and Lactate Dehydrogenase	FAS	Repeat
14.2.12	Duration of RECIST Response by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.13	Time to First New Anticancer Treatment by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.14	Summary of 18F-DCFPyL Maximum Standardized Uptake Value (SUVmax) from Baseline by Study Visit	FAS	Unique
14.2.15	Summary of 18F-DCFPyL Positive Lesion Counts from Baseline by Study Visit	FAS	Unique
14.2.16.1	Summary of FACT-P Scores by Study Visit	FAS	Unique
14.2.16.2	Summary of SF-12 Component Scores by Study Visit	FAS	Unique
14.2.16.3	Summary of EQ-5D Scores by Study Visit	FAS	Unique
14.2.16.4	Summary of aBSI Scores by Study Visit	FAS	Unique
14.2.16.5	Summary of ECOG Performance Scores by Study Visit	FAS	Unique
14.2.16.6	Summary of Brief Pain Inventory Scores by Study Visit	FAS	Unique
14.2.17	Time to First Symptomatic Skeletal Event	FAS	Unique
14.2.18	Incidence of Pain Progression	FAS	Unique

Figures

#	Title	Population	Comment
14.2.5.1.1	Mean (+ SD) of Serum PSA (Primary Efficacy Endpoint) Values by Study Week by Randomized Treatment Group and Risk Stratification	FAS	Unique
14.2.5.1.2	Mean (+/- SD) of Change from Baseline PSA (Primary Efficacy Endpoint) (ng/dL) by Study Week by Randomized Treatment Group and Risk Stratification	FAS	Repeat
14.2.11.1.1	Radiographic Progression Free Survival Kaplan-Meier Curve	FAS	Unique
14.2.9.1.1	Overall Survival Kaplan-Meier Curve	FAS	Repeat
14.2.10.1.1	Time to PSA Progression Kaplan-Meier Curve	FAS	Unique
14.2.12.1	Duration of RECIST Response Kaplan-Meier Curve	FAS	Unique
14.2.13.1	Time to First New Anticancer Treatment Kaplan-Meier Curve	FAS	Unique
14.2.5.1.3	Waterfall Plot by Randomized Treatment Group of Best Confirmed PSA Decline (%) from Baseline	FAS	Unique
14.2.5.1.4	Waterfall Plot by Randomized Treatment Group of Best PSA Decline from Baseline(%), Any Measurement	FAS	Unique

Listings

#	Title	Population	Comment
16.2.1.1	Subject Enrollment Information and Study Populations	Enrolled	Unique
16.2.1.2	Subject Disposition	Safety	Unique
16.2.3	Subjects who did not Satisfy Eligibility Criteria	Screening Failure	Unique
16.2.2.2	Protocol Deviations	Safety	Unique

16.2.5.1	Study Drug Administration	Safety	Unique
16.2.5.2	Enzalutamide Administration	Safety	Unique
16.2.7.1	Treatment-Emergent Adverse Events	Safety	Unique
16.2.7.2	Subjects Withdrawn Due to TEAEs	Safety	Repeat
14.3.2.1	Serious Treatment-Emergent Adverse Events	Safety	Repeat
14.3.2.2	Deaths	Safety	Unique
16.2.8.1	Hematology Results	Safety	Unique
16.2.8.2	Clinical Chemistry Results	Safety	Repeat
16.2.8.3	Serum PSA Results	Safety	Repeat
16.2.8.4	Urinalysis Results	Safety	Repeat
14.3.4	Dose Limiting Toxicities for I-131-1095 Treated Subjects with CTCAE Grades >= 3	Safety	Unique
16.2.9	Vital Signs Data	Safety	Unique
16.2.10	ECG Data	Safety	Unique
16.2.4.1	Subject Demographic and Baseline Characteristics	Safety	Unique
16.2.4.2	Prostate Cancer History	Safety	Unique
16.2.4.3	Medical and Surgical History	Safety	Unique
16.2.4.4	Cancer-Related Radiation History	Safety	Unique
16.2.4.5	Prior Anticancer Therapy for Non-Prostate Cancer	Safety	Unique
16.2.4.6	Prior Systemic Anticancer Therapy for Prostate Cancer	Safety	Unique
16.2.4.7	Prior and Concomitant Medications	Safety	Unique
16.2.4.8	Concurrent Procedures	Safety	Unique
16.2.6.1	Primary Endpoint Responses	FAS	Unique
16.2.6.2	Radiographic Progression Free Survival	FAS	Unique
16.2.6.3	Time to PSA Progression	FAS	Unique
16.2.6.4	Duration of Response	FAS	Unique
16.2.6.5	Time to First New Anti-Cancer Therapy	FAS	Unique
16.2.6.6	Overall Survival	FAS	Unique
16.2.6.7	PSMA-Positive Lesion Counts	FAS	Unique
16.2.6.8	PSMA Avidity	FAS	Unique
16.2.6.9	Bone Scans	FAS	Unique

16.2.6.10	Bone Scan Assessments	FAS	Unique
16.2.6.11	Target Lesions	FAS	Unique
16.2.6.12	Non-Target Lesions	FAS	Unique
16.2.6.13	New Lesions	FAS	Unique
16.2.6.14	RECIST Responses	FAS	Unique
16.2.6.15	Lesion SUVmax Values	FAS	Unique
16.2.6.16	SF-12 Health Survey Results	FAS	Unique
16.2.6.17	FACT-P Scores	FAS	Unique
16.2.6.18	aBSI Scores	FAS	Unique
16.2.6.19	BPI-SF Scores	FAS	Unique
16.2.6.20	EQ-5D-5L Scores	FAS	Unique
16.2.6.21	ECOG Performance Status	FAS	Unique