Statistical Analysis Plan J5T-OX-JXCA Version 3

A Phase 3, Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)

NCT04647526

Approval Date: 26-Jul-2024

POINT BioPharma

STATISTICAL ANALYSIS PLAN

SPLASH: **S**tudy Evaluating Metastatic Castrate Resistant **P**rostate Cancer Treatment Using [**L**u-177]-PNT2002 PSMA Therapy **A**fter **S**econd-Line **H**ormonal Treatment
Protocol Number: PBP-301

Version:	Date:
Version 3.0	26JULY2024

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DOCUMENT HISTORY

Version	Date	Description
1.0	31AUG2022	New Document
2.0	01NOV2023	Updates: • Text edits throughout for clarity and/or consistency. • Clarification on PK Analysis substudy subjects that will be enrolled after the end of the randomization phase in Section 2.2 and Section 3.2. • Clarification on baseline derivation for safety evaluation of randomized treatment subject for subjects who did not receive treatment in Section 3.1.5. • Removal of the requirement that ITT subjects be in the Imaging Analysis Set in Section 3.2. • Added clarifying footnote regarding missed bone scans in Table 3 in Section 3.3.1.1. • Clarification of how adjudication results will be handled for rPFS if there are multiple assessments with adjudication in Section 3.3.1.2. • Clarifications to how assessments will be counted for rPFS when only one of either bone lesion or soft tissue response was assessed and not both in Section 3.3.1.2. • CCI [redacted] • Added text clarifying how visits with missing bone scans would be analyzed for ORR in Section 3.3.2.2. • Clarified that PSA response after receiving a new anticancer therapy therapy will not be included in the analysis of PSA response rate (Section 3.3.3.2). • Removal of death as censoring or event from SSRE (Section 3.3.2.3), bPFS (Section 3.3.3.3), and deterioration by CCI [redacted] (Section 3.3.5.2). • Added renal impairment status at baseline and PSMA-avidity criteria version used to rPFS subgroups (Section 3.8.1) • Specified additional RPSFTM analysis in Section 3.8.2.1.

		• Changed method for objective response rate analysis from the stratified Cochran–Mantel–Haenszel test to a stratified logistic regression model in Section 3.8.2.2. The same change is made for PSA response rate in Section 3.8.3.2. • Analysis of concordance between BICR and Investigator Assessments was added in Section 3.8.3.4. • Addition of definition of treatment emergent period for crossover in Section 3.9. • Removal of confidence intervals from AE tables in Section 3.9.1.1. • Addition of windowing definition to be used in by visit analyses in Section 3.9 and Section 3.10. • Addition of imaging agents subset analysis in Section 3.12.
3.0	01APR2024	• Addition of the exploratory rPFS analysis. • Addition of CCI [redacted] • Addition of CCI [redacted] • Addition of CCI [redacted]
	18JULY2024	• Clarification of the alpha spending for OS analyses

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
AE	adverse event
CCI	[redacted]
ARAT	androgen receptor axis-targeted
ATC	Anatomical Therapeutic Chemical
BICR	blinded independent central review
BMI	body mass index
BOR	best objective response
CCI	[redacted]
bPFS	biochemical progression-free survival
C1D1	cycle 1, day 1
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CSR	clinical study report
CSPC	castration-sensitive prostate cancer
CTCAE	Common Terminology Criteria for Adverse Events
CT/MRI	computed tomography/magnetic resonance imaging
DAS	Dosimetry Analysis Set
DCO	Data Cut-off
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EOT	end of treatment
CCI	[redacted]
FDG-PET	fluorodeoxyglucose-positron emission tomography
FPI	First patient in
CCI	[redacted]
iDSMB	independent Data Safety Monitoring Board
ITT	Intent to Treat
mCRPC	metastatic castration-resistant prostate cancer
NTL	Non-target lesion
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease
PK	pharmacokinetic
PPAS	Per Protocol Analysis Set
PR	partial response
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
PSMA-PET	prostate-specific membrane antigen-positron emission tomography
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFTM	rank preserving structural failure time models
rPFS	radiological progression free survival

RSAS	Randomization Safety Analysis Set
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	Standardised MedDRA Query
SOA	Schedule of Activities
SOC	system organ class
SOD	sum of the diameter
SSRE	symptomatic skeletal-related event
SUV	standard uptake value
TEAE	treatment-emergent adverse event
TOI	Trial Outcome Index
TL	Target lesion

1 INTRODUCTION

The SPLASH study is a Phase 3 multicenter, open-label, randomized trial evaluating the efficacy and safety of CCI prostate-specific membrane antigen (PSMA) targeted radioligand [Lu-177]-PNT2002 in subjects with metastatic castration-resistant prostate cancer (mCRPC) who have progressed on androgen receptor axis-targeted (ARAT) therapy.

The statistical analysis plan (SAP) contains a detailed description of the data presentations and statistical analyses that will be included in the clinical study report (CSR) for SPLASH. The statistical methods and analyses described here are based on those presented in the study protocol version 4.0, dated 23 Nov 2022. CCI The SAP is updated accordingly. CCI

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2 STUDY SUMMARY

2.1 Study Objectives

The overall objective of this trial is to determine the efficacy, safety, dosimetry, and pharmacokinetic (PK) profile of CCI PSMA-targeted radioligand [Lu-177]-PNT2002 in subjects with mCRPC who have experienced disease progression on ARAT therapy.

Primary Efficacy objective:

- To determine the efficacy of [Lu-177]-PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression in subjects with mCRPC who have progressed on ARAT.

Secondary Efficacy objectives:

- To assess the radiographic response to [Lu-177]-PNT2002 versus abiraterone or enzalutamide.
- To determine the effect of [Lu-177]-PNT2002 versus abiraterone or enzalutamide on overall survival in subjects who have progressed on ARAT.
- To determine the effect of [Lu-177]-PNT2002 versus abiraterone or enzalutamide on developing a symptomatic skeletal-related event.
- To determine the effect of [Lu-177]-PNT2002 versus abiraterone or enzalutamide on prostate-specific antigen (PSA) kinetics in subjects who have progressed on ARAT.

Safety objective:

- To evaluate the safety and tolerability of [Lu-177]-PNT2002 versus abiraterone or enzalutamide.

Exploratory objectives:

2.2 Study Design

The SPLASH study is a Phase 3, multicenter, open-label, randomized trial with a safety and dosimetry lead-in phase evaluating the efficacy and safety of CCI PSMA targeted radioligand [Lu-177]-PNT2002 in subjects with mCRPC who have progressed on ARAT therapy. Approximately 70 sites are planned in Canada, the United States, the European Union, and the United Kingdom. The study consists of three phases: Dosimetry, Randomized Treatment, and Long-term Follow-up Phase.

Dosimetry Phase

The planned enrollment for the Dosimetry Phase will be 25 subjects. Subjects who meet all eligibility requirements will be administered 6.8 GBq (±10%) of [Lu-177]-PNT2002 every 8 weeks for 4 cycles. After each of the 4 treatment cycles, subjects will be assessed every 2 weeks until Week 32 (8 weeks after last cycle) to monitor tolerability and safety. The independent Data Safety Monitoring Board (iDSMB) will be convened to evaluate safety results after the first five subjects have completed their first treatment cycle, after 15 subjects have completed their first treatment cycle, and once all 25 subjects have completed their first treatment cycle. Unscheduled meetings may be requested by the Medical Monitor if there are safety concerns.

Efficacy will be assessed during the Dosimetry Phase based on radiographic tumor assessments, PSA blood samples, Eastern Cooperative Oncology Group (ECOG) status, and CCI Radiographic response will be collected and assessed by BICR throughout the Dosimetry Phase.

Randomized Treatment Phase

Once dosimetry and safety data are generated to confirm the selected dose meets pre-specified criteria outlined in protocol Section 5.7.2 and the iDSMB has provided an approval to proceed, the Randomized Treatment Phase will commence. The Randomized Treatment Phase will open to US sites after all subjects in the Dosimetry Phase have completed the treatment follow-up period (i.e., 8 weeks after last dose) or earlier if FDA agreement is obtained. Randomization will occur in a 2:1 ratio in the following groups:

- Arm A, in which 260 subjects will receive [Lu-177]-PNT2002.
- Arm B, in which 130 subjects will receive enzalutamide (160 mg orally qd) or abiraterone (1000 mg orally qd with: 5 mg bid prednisone or 0.5 mg qd dexamethasone).

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Treatment Arm A

Subjects in Arm A will receive 6.8 GBq (±10%) of [Lu-177]-PNT2002 every 8 weeks for 4 cycles. Subjects will be assessed every 2 weeks until completion of the treatment phase (End of Treatment [EOT]; 8 weeks after last dose). In the absence of Blinded Independent Central Review (BICR)-assessed radiographic progression by EOT, subjects will continue to be followed every 8 weeks until radiographic progression by BICR and follow all procedures indicated within the SOA for their Progression Visit.

A subset of up to [redacted] subjects will be evaluated for PK in Arm A (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada.

Treatment Arm B

Subjects randomized to Arm B will receive abiraterone or enzalutamide as defined below:

- For subjects progressing on either enzalutamide, darolutamide, or apalutamide, administer abiraterone according to the approved product labeling of 1000 mg qd plus prednisone at a dose of 5 mg bid.
- For subjects progressing on abiraterone, administer either:
  - Enzalutamide prescribed according to the approved product labeling of 160 mg qd **or**
  - Abiraterone prescribed according to the approved product labeling of 1000 mg qd plus dexamethasone at a dose of 0.5 mg qd.

Subject's treatment must remain the same throughout the Treatment Phase with the exception of dose modifications in accordance with product labeling.

Subjects in Arm B will be assessed every 4 weeks until completion of the treatment phase (End of Treatment [EOT]; 8 weeks after last dose). In the absence of Blinded Independent Central Review (BICR)-assessed radiographic progression by EOT, subjects will continue to be followed every 8 weeks until radiographic progression by BICR and follow all procedures indicated within the SOA for their Progression Visit.

Subjects in Arm B who experience radiographic progression per BICR, have not started an intervening treatment, and have no uncontrolled adverse events (AEs) will be eligible for consent to crossover to receive 6.8 GBq (±10%) of [Lu-177]-PNT2002 every 8 weeks for 4 cycles. Subjects will be followed for safety and assessment of second progression by the investigator.

An iDSMB will monitor ongoing safety data (AEs/serious AEs (SAEs), electrocardiograms (ECGs), laboratory test results) in Arms A and B on a quarterly basis throughout the Randomized Treatment Phase.

Long-Term Follow-up Phase

The Long-Term Follow-up Phase for all subjects consists of a phone call or a planned clinic visit every 3 months to assess survival status, late-radiation related toxicities (for subjects who received [Lu-177]-PNT2002), new anticancer therapies, and progression following any new therapy for at least 5 years from cycle 1, day 1 (C1D1) (if subjects crossover, 5 years from the first dose of [Lu-177]-PNT2002) to death, or loss to follow up).

2.2.1 Number of Subjects

The planned enrollment for the Dosimetry Phase will be 25 subjects.

In the Randomized Treatment Phase, 390 subjects are planned to be randomized in a 2:1 ratio (260 subjects to receive [Lu-177]-PNT2002 treatment versus 130 subjects to receive abiraterone or enzalutamide).

The overall planned enrollment is approximately 435 subjects including the additional PK Analysis Set.

Sample Size Estimation

The sample size estimation is based on the primary endpoint rPFS. In total, CCI rPFS events provide approximately CCI power to test the alternative hypothesis of hazard ratio (HR) CCI at an α of CCI (one-sided). The HR of CCI corresponds to an improvement in the median progression free survival from CCI months with the control to CCI months with [Lu-177]-PNT2002, assuming rPFS is exponentially distributed. The rPFS power calculations are based on a log-rank test. A total of 390 patients are expected to be accrued assuming that the trial will have CCI months of uniform accrual and an overall study duration up to CCI months. A 20% dropout rate is assumed (exponential dropout rate of CCI). The final analysis of rPFS will be performed when CCI patients experience radiological progression or die.

2.2.2 Randomization Procedures

In the Randomized Treatment Phase, randomization will occur in a 2:1 ratio for the [Lu-177]-PNT2002 treatment arm versus abiraterone or enzalutamide. Upon determination of a subject's eligibility, including PSMA avidity confirmation by BICR, randomization will be performed using Interactive Web Response System (IWRS).

CCI [redacted]

2.2.3 Stopping Rules

Stopping rules apply to both the Dosimetry and Randomized Treatment Phases. The study will be suspended and possibly stopped for any of the following reasons:

- Death in any subject in which the cause of death is unexpected and assessed as at least possibly related to [Lu-177]-PNT2002 and deemed in the judgement of the Sponsor to contraindicate further dosing of study subjects.
- Any treatment-related event, in the judgment of the Medical Monitor, deemed serious enough to warrant immediate review by the iDSMB. This may include any treatment-related symptomatic and/or irreversible treatment-related grade 4 hematologic toxicity, nephrotoxicity, lacrimal gland toxicity (e.g., dry eyes), or salivary gland toxicity (e.g., xerostomia).
- Any other safety finding assessed as related to [Lu-177]-PNT2002 that, in the opinion of the iDSMB or Sponsor, contraindicates further dosing of study subjects.

2.2.4 Efficacy Assessments

All subjects will undergo disease assessments by whole body bone scans and computed tomography/magnetic resonance imaging (CT/MRI) of the chest, abdomen, and pelvis (as described in Protocol Section 7.8.1). Subjects will also be evaluated for changes in ECOG status, PSA measurements by a central laboratory, CCI [redacted] and skeletal events review. Schedule of Activities (SOA) Table 1 (Dosimetry), Table 2 (Arm A) and Table 3 (Arm B) are presented in the study protocol.

2.2.4.1 Progression

2.2.4.1.1 Radiographic Progression

Determination of radiographic progression will be performed by the BICR on the basis of conventional imaging performed as per the SOAs.

2.2.4.1.2 CT and MRI Tumor Assessment

CT or MRI images of the chest, abdomen, and pelvis will be used to assess for progression as per PCWG3-modified RECIST 1.1 criteria, with other areas of disease investigated based on the signs and symptoms of individual patients. Nodal and visceral disease progression will be determined as per PCWG3-modified RECIST 1.1 criteria.

2.2.4.1.3 Bone Scans

Progression of bone disease will be determined as per PCWG3 criteria.

2.2.4.1.4 Biochemical Progression

Biochemical progression will be defined as the first PSA increase from baseline ≥25% and ≥ 2 ng/mL above nadir confirmed by a second PSA measurement with an increase from baseline ≥25% and ≥ 2 ng/mL above nadir at least 3 weeks later per PCWG3.

2.2.4.1.5 Unequivocal Clinical Progression

Clinical progression is defined as the lack of further benefit to the subject from [Lu-177]-PNT2002 treatment or control arm treatment alone by one or more of the following:

- Initiation of chronic opioid use for new onset of prostate cancer pain suspected due to disease progression defined as daily use for more than 7 consecutive days or more than 10 days within a 14-day period, or
- Immediate need to initiate cytotoxic chemotherapy for prostate cancer, or
- ECOG performance status deterioration to ≥3 due to prostate cancer, or
- Radiation or surgical therapy for complications of prostate cancer tumor progression, excluding palliative radiotherapy (in treatment of pain at site of bone metastases present at baseline, unless indicative of disease progression).

2.2.4.4 Symptomatic Skeletal-Related Event

The occurrence of one or more of the following should be considered a symptomatic skeletal-related event (SSRE):

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation is required.
- Orthopedic surgical intervention for bone metastasis.

2.2.5 Safety Assessments

Safety will be assessed by measurement of weight, physical examinations, vital signs, ECGs, blood chemistry and hematologic parameters, review of AEs/SAEs, and review of concomitant medications. Safety assessments are described in Protocol Section 7.9. Schedule of Activities are shown in the protocol: Table 1 for the Dosimetry Phase, Table 2 for Arm A, and Table 3 for Arm B.

2.2.6 Dosimetry Analysis

Dosimetry analysis is not part of the scope of this SAP and will be described in a separate document and performed by another vendor.

2.2.7 PK Assessments

The PK Substudy will be performed on up to CCI subjects in Arm A at selected sites on the first treatment cycle of [Lu-177]-PNT2002. Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. PK

samples from both blood and urine will be collected to measure radioactivity. The PK analysis will be performed and reported separately and analysis method is not described in this SAP.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher.

3.1.2 Reporting of Numerical Values

Key data collected in the database will be presented in data listings. Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum by treatment group. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Confidence intervals (CIs) will be provided where appropriate. Categorical variables will be summarized using frequency counts and percentages by treatment group. Percentages will be based on the total number of subjects. If there are missing values, the number and the percentage missing will be presented. For binomial proportions within each arm, CIs will be calculated using Clopper-Pearson exact method unless otherwise specified.

Means, medians, and CIs will be reported to one decimal place more than the data reported (e.g., on the electronic case report form (eCRF) or by the laboratory/vendor). Standard deviations will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places displayed (e.g., on the eCRF or by the laboratory/vendor). For PSA and treatment dose, minimum and maximum will be reported to 2 decimal places. P-values will be reported to 4 decimal places. For lab values of the form of "<x" (i.e., below the lower limit of quantification) or ">x" (i.e., above the upper limit of quantification), the values will be imputed as "x".

3.1.3 Statistical Testing and Multiplicity Control

This study has one primary endpoint, radiological progression-free survival (rPFS), which will be tested at α = CCI (one-sided). If the rPFS test is significant then three secondary endpoints will be tested using the fixed sequence method for controlling the α. Significance testing will occur in the following sequence: rPFS (primary endpoint), overall survival (OS) (secondary endpoint), objective response rate (ORR) (secondary endpoint), and Time to Symptomatic Skeletal Related Event (SSRE), moving to the next endpoint only after a statistically significant difference between the 2 arms is established at α=CCI (one-sided) on the previous endpoint.

CCI [redacted] For OS, the interpolated spending function will be used to control an overall type I error rate of CCI (one-sided), CCI [redacted] No further testing will occur once an endpoint in the sequence fails to show significance, and analyses for that endpoint and all subsequent endpoints will be considered descriptive. The timing of each look will be discussed in Section 3.8.2.

The p-values presented for other secondary and exploratory endpoints will not be adjusted for multiplicity and will be considered descriptive in nature.

3.1.4 Investigational Product and Study Treatment

Investigational products in this study are [Lu-177]-PNT2002 and ^{18}F-DCFPyL and ^{68}Ga-PSMA-11 as PSMA imaging agents. Study treatment refers to [Lu-177]-PNT2002, abiraterone, or enzalutamide.

3.1.5 Baseline Value, Change from Baseline, and Percent Change from Baseline

For safety evaluation of imaging agents, the baseline value is defined as the last non-missing value obtained prior to administration of ^{18}F-DCFPyL or ^{68}Ga-PSMA-11. This applies to all subjects taking imaging agents in either the Dosimetry or Randomized Treatment Phases.

For demographic/disease characteristic, safety and efficacy evaluation in the dosimetry phase (single arm), baseline value is defined as the last non-missing value obtained prior to administration of first dose of study treatment ([Lu-177]-PNT2002).

For demographic/disease characteristic and efficacy evaluation of randomized treatment, the baseline value is defined as the last non-missing value, including unscheduled assessment, on or before the date of randomization. For efficacy endpoints with the first assessment conducted post randomization but before first dose of study treatment, such as PRO endpoints, the baseline value is defined as the last non-missing value prior to administration of first dose of study treatment ([Lu-177]-PNT2002, abiraterone, or enzalutamide).

For safety evaluation of randomized treatment, the baseline value is defined as the last non-missing value prior to administration of first dose of study treatment ([Lu-177]-PNT2002, abiraterone, or enzalutamide) or the last non-missing value on or before the date of randomization if the study treatment was never received. For assessments taken on the day of first dose where time is not captured, assessments will be considered pre-dose if such procedures are required by the protocol to be conducted before first dose, unless there is indicator suggest the other way.

For subjects randomized to Arm B who received [Lu-177]-PNT2002 upon BICR confirmed progression, the baseline value in the cross-over period is defined as the last non-missing value prior to administration of first dose of [Lu-177]-PNT2002.

Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each subject (i.e., post-dose – baseline). Percent change from baseline will be calculated as [(post-dose – baseline)/baseline]*100.

3.1.6 Handling of Missing/Incomplete Values

Missing or incomplete medication start and end dates will be imputed to identify concomitant medications. Missing or incomplete AE start dates will be imputed to determine treatment-emergent AEs. Otherwise, missing data will not be imputed and observed cases will be used in the analyses.

3.2 Analysis Sets

For identifying subjects who are screened for the Dosimetry and Randomized Treatment Phases of the study, the phases will be separated based on informed consent date entered into the EDC. Dosimetry subjects are those with informed consent dates prior to October 6, 2021, and Randomized Phase subjects are those with informed consent dates on or after this date.

Imaging Analysis Set

The Imaging Analysis Set consists of all subjects who provide written informed consent and receive at least one dose of ^{68}Ga-PSMA or ^{18}F-DCFPyL. The subjects in the Imaging Analysis Set will be presented separately for the Dosimetry and Randomized Treatment Phases, unless otherwise specified.

Dosimetry Analysis Set – Part 1

The Dosimetry Analysis Set (DAS) comprises all subjects in the Imaging Analysis Set who receive at least one dose of [Lu-177]-PNT2002 in Part 1 of the study. The DAS will be used for all analyses in Part 1 of the study.

Intent to Treat Analysis Set – Part 2

The Intent to Treat (ITT) Analysis Set comprises all subjects who are randomized. The ITT Analysis Set will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received and will be the primary analysis set for all efficacy analyses.

Per Protocol Analysis Set – Part 2

The Per Protocol Analysis Set (PPAS) contains all subjects from the ITT Analysis Set who receive at least one dose of study treatment ([Lu-177]-PNT2002 abiraterone, or enzalutamide) during the randomization phase of the trial, have at least one post-baseline tumor assessment, and do not have any exclusionary protocol violations that would affect the evaluation of the primary endpoint. These protocol violations include but are not limited to violations of inclusion/exclusion criteria deemed to impact efficacy, inadequate study drug compliance over the dosing period as determined from the dosing information in the eCRF, usage of prohibited concomitant medications, and incorrect randomization. Additionally, other relevant criteria for exclusion from the PPAS, such as early termination or interruption of treatment, may be identified for review.

Prior to the database lock for the primary rPFS analysis in Part 2, all major protocol deviations will be reviewed by study team in determining PPAS exclusions. Subject ID will be blinded to reviewers in making the determination. Reasons for exclusion from the PPAS will be documented for each subject excluded.

Randomization Safety Analysis Set – Part 2

The Randomization Safety Analysis Set (RSAS) comprises all subjects in the ITT Analysis Set who receive at least one dose of study treatment ([Lu-177]-PNT2002, abiraterone, or enzalutamide) during the randomization phase of the trial. The RSAS will be analyzed based on the actual treatment received. All safety analyses in Part 2 of the study will be conducted using the RSAS.

PK Analysis Set

All subjects who have received at least one dose of [Lu-177]-PNT2002 and provided at least one post-dose analyzable sample for PK analysis will be included in the PK analysis set.

Non-Randomized PK Substudy Safety Set

All subjects who were not included in the RSAS and received at least one dose of [Lu-177]-PNT2002 as part of the PK Substudy will be included in the non-randomized PK Substudy safety set. AEs for these subjects will be listed. These subjects will not be included in any other safety or efficacy presentations.

3.3 Analysis Endpoints

3.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is radiographic Progression Free Survival (rPFS). rPFS is defined as the time from the reference date to progression on soft tissue by RECIST v1.1, confirmed progression on bone lesions by PCWG3, or death from any cause, whichever occurs first. For the Randomized Treatment Phase, the reference date is the randomization date. For the Dosimetry Phase, the reference date is the enrollment date. The date of disease progression will be the date of the scan for the first objectively documented PD per RECIST v1.1 or PCWG3. CCI [redacted] Selected sensitivity analyses will be conducted using investigator-assessed tumor response.

3.3.1.1 Overall Radiological Response per Visit (RECIST/PCWG3)

Each subject's visit response on soft tissue will be determined using RECIST tumor response criteria version 1.1, by BICR and also by the investigator (RECIST 1.1 criteria, Eisenhauer et al., 2009):

Target Lesions (TLs) will be evaluated at post-baseline visits as follows:

- Complete Response (CR):
  - Disappearance of all target lesions.
  - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Progressive Disease (PD):

  - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
  - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  - The appearance of one or more new lesions is also considered progression.
- Not Evaluable (NE): Missing or incomplete lesion measurements.
- Not Applicable (NA): No target lesions at baseline.

Non-Target Lesions (NTLs) will be evaluated at post-baseline visits as follows:

- Complete Response (CR):
  - Disappearance of all non-target lesions.
  - All lymph nodes must be <10mm in short axis.
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s).
- Progressive Disease (PD):
  - Unequivocal progression of existing non-target lesions. To achieve 'unequivocal progression' there must be an overall level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy.
  - The appearance of one or more new lesions is also considered progression.
- Not Evaluable (NE): Missing or incomplete lesion measurements.
- Not Applicable (NA): No non-target lesions at baseline.

The overall soft tissue response at each visit will be determined combining the TL and NTL responses and new lesion information at the visit as specified in Table 1 below.

Table 1. Overall Soft Tissue Visit Response (RECIST 1.1)

Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD[a] or NE	No	PR
SD	Non PD[a] or NE	No	SD
NA	Non CR/Non PD	No	SD
NA	NA	No	NED
NE	Non PD[a] or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD

[a]Non PD = CR or Non CR/Non PD or NA.
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL and/or NTLs at baseline), NED = No Evidence of Disease (only relevant when there is no TL and NTL from baseline).

Bone lesions will be evaluated by BICR and also by the investigator using PCWG3 as specified in Protocol Appendix 2, which is listed in Table 2 below as well. Specifically, progression on a bone scan is identified:

- For the first post-treatment scan (Week 8 or earlier unscheduled assessment), bone progression is defined as at least two new lesions compared to the baseline assessment, with at least two additional lesions seen on the next confirmatory scan. The date of progression is the date of the first post-treatment scan when the first two new lesions were documented.
- For scans after the first post-treatment scan, bone progression is defined as at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan (persistence of lesions or increase in lesions), with the confirmatory scan performed preferably no later than the next scheduled bone scan. The date of progression is the date of the scan prior to the confirmatory scan that first documents the new lesions.

Table 2. Bone Progression Status Categories (PCGW3)

Non Progressive Disease (Non-PD)	No evidence of progression, or appearance of one new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progression.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression.
Not Evaluable (NE)	Only relevant if no evaluable follow-up bone scan is available
PD unconfirmed (PDu)	Placeholder when PD is presumed. Updated based on next scan. If final visit, change to Non-PD.

The overall radiological response at each visit will be determined combining the overall soft tissue response and bone progression status at the visit as specified in Protocol Appendix 3 and in Table 3. Overall Radiological Visit Response (RECIST/PCWG3) below

Table 3. Overall Radiological Visit Response (RECIST/PCWG3)

Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Bone lesions at visit Present/Absent	Overall radiological visit response
CR	Non-PD	Absent	CR
CR	Non-PD	Present	PR
CR	NE*	-	PR
PR	Non-PD or NE*	Any	PR
SD	Non-PD or NE*	Any	SD
NED	Non-PD	Any	Non-PD
NED	NE	Any	NE
NE	Non-PD or NE	Any	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any (except PD)	PDu	Any	PDu

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable (if an assessment is missing, it will be considered NE), NED = No Evidence of Disease (only relevant if there were no TL and NTLs at all visits), PDu = Placeholder when PD is presumed for bone assessment. Updated based on next scan. If final visit, change to Non-PD.
* Visits with a missing bone scan and RECISIT 1.1 response of other than PD will be considered to have an overall radiological response of NE for the analysis unless the subject has a PCWG3 response of Non-PD at a subsequent visit.

3.3.1.2 Primary Endpoint – Radiological Progression Free Survival (rPFS)

Radiological progression-free survival is defined as the time from the reference date to progression by RECIST v1.1 or confirmed progression on bone scan assessed by PCWG3, or death from any cause, whichever occurs first. For the Randomized Treatment Phase, the reference date is the randomization date. For the Dosimetry Phase, the reference date is the enrollment date.

The BICR efficacy read will be conducted according to a double radiologist review paradigm, where two radiologists perform BICR for a given subject and a third radiologist will adjudicate discordant assessments. CCI

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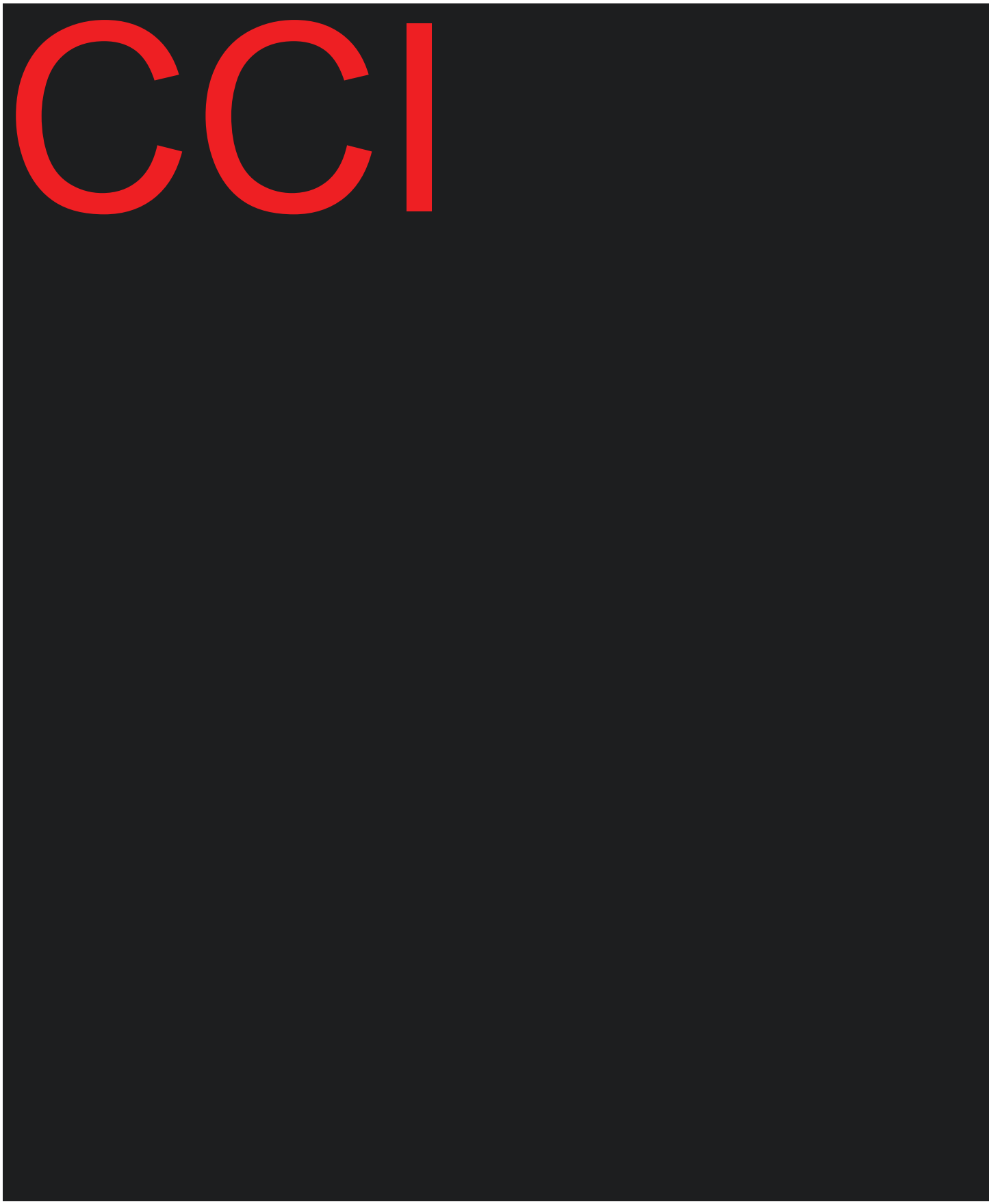


3.3.2 Key Secondary Efficacy Endpoints

3.3.2.1 Overall survival (OS)

Overall survival is defined as the time from the reference date to the date of death from any cause. Subjects who did not die at the time of the analysis will be censored at the date the subject was last known to be alive using all available data entered on the eCRF. For the Randomized Treatment Phase, the reference date is the randomization date. For the Dosimetry Phase, the reference date is the enrollment date. CCI

If a death is reported with a partial death date, missing components death date will be imputed as below:

- If the month is missing, use January as the imputed month.
- If the day is missing, use 01 as the imputed date.
- Compare the imputed death date vs. the subject's last know alive date + 1, and select the latest as the final imputed death date.

3.3.2.2 Objective Response Rate (ORR)

The primary analysis for ORR is the confirmed ORR assessed by BICR out of all subjects with measurable disease (target lesions) at baseline. A subject will be classified as a confirmed responder if the RECIST 1.1 criteria for a confirmed CR or PR (a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed) are satisfied in the absence of confirmed progression on bone scan assessed by PCWG3 between the two visits. Subjects who respond after receiving a new anticancer therapy will not be considered as responders. Subjects who respond per RECIST 1.1 with a bone scan missing at the visit followed by a confirmed bone PD at next visit will not be considered as responders. For each treatment group, the confirmed ORR is the number of subjects who

received a confirmed CR or PR (i.e., initial and confirmatory responses of CR-CR, PR-CR, or PR-PR) divided by the number of subjects in the treatment group with measurable disease at baseline. BICR selected reader in rPFS analyses will be used in baseline measurable disease set or evaluable disease set designations.

In the case where a subject has two non-consecutive visit responses of PR, as long as the time between the 2 visits of PR is at least 4 weeks and there is no PD between the PR visits, the subject will be defined as a confirmed responder. Similarly, if a subject has visit responses of CR, NE, CR, as long as the time between the 2 visits of CR is at least 4 weeks, a best confirmed response of CR will be assigned.

3.3.2.3 Time to Symptomatic Skeletal-Related Event (SSRE)

Time to first symptomatic skeletal-related event is defined as the time from reference date to first symptomatic skeletal-related event as defined in Section 2.2.4.4. For the Randomized Treatment Phase, the reference date is the randomization date. For the Dosimetry Phase, the reference date is the enrollment date. Subjects who have not experienced any SSRE will be censored at the last SSRE evaluation before crossover. Subjects without an SSRE evaluation after the reference date will be censored at the reference date.

3.3.3 Secondary Efficacy Endpoints

3.3.3.1 Duration of response (DoR)

Duration of Response will be defined as the time from the date of first documented confirmed CR or PR (by BICR using RECIST 1.1 and in the absence of confirmed progression on bone scan by PCWG3) to the date of first documented radiographic progression (by BICR) or death: DoR = (Date of first documented progression/death/censor – Date of first documented confirmed response + 1). Subjects who have attained CR or PR as the best overall response, did not have progressive disease, and did not die will be censored on the primary rPFS censoring date.

3.3.3.2 PSA Response Rate

Confirmed PSA response rate will be defined as the proportion of subjects achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second PSA reduction ≥50% at least 3 weeks later. A patient will be regarded as having a single PSA response if their PSA level at any post-baseline visit is reduced by 50% or more compared with baseline. For each treatment group, the PSA response rate is the number of subjects with a PSA response divided by the number of subjects in the treatment group. Subjects achieving PSA response after receiving a new anticancer therapy or post crossover will not be considered as responders.

3.3.3.3 Biochemical Progression-free Survival (bPFS)

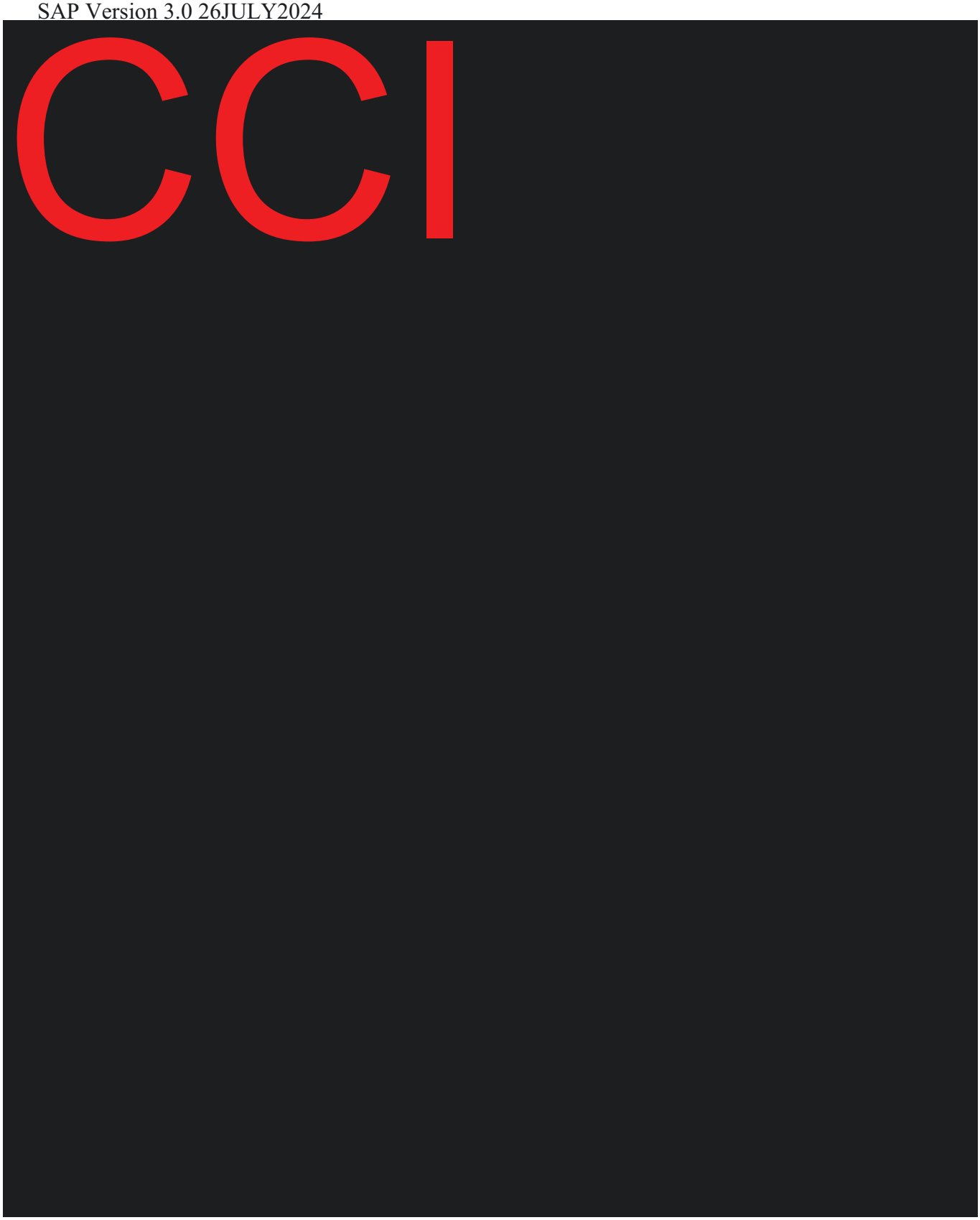
Biochemical progression-free survival (bPFS) is defined as time from the date of randomization/enrollment to the date of the first PSA increase from baseline ≥25% and ≥ 2 ng/mL above nadir confirmed by a second PSA measurement at least 3 weeks later per PCWG3. Subjects who do not progress, including those who withdraw from the study or are lost to follow-up, will be censored at the date of last valid PSA measurement from a scheduled or unscheduled

visit. Rises in PSA within the first 12 weeks of date of first dose of randomized treatment will be ignored. Subjects with a new cancer therapy will be censored at the last PSA assessment prior to the start of the new cancer therapy.

3.3.4 Safety Endpoints

- Frequency and severity of adverse events and serious adverse events graded using Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0.
- Changes from baseline in physical exam findings, vital signs, clinical laboratory values, and ECG values.
- Number of subjects discontinuing study drug due to adverse events.

3.3.5 Exploratory Endpoints



3.4 Subjects Disposition and Evaluability

Subject disposition will be summarized separately for subjects in the Dosimetry Phase and for subjects in Arms A and B of the Randomized Treatment Phase.

3.4.1 Subject Disposition

For both the Dosimetry and Randomized Treatment Phases, the number of subjects screened, the number and percentage of subjects who do not receive the imaging agent, and the number and percentage who do receive the imaging agent (i.e., are in the Imaging Analysis Set) will be presented. Among those who did not receive the imaging agent, the categories of reason for screen failure will be presented with percentages based on the number screened. For the Dosimetry Phase, the subjects in the Imaging Analysis Set who did not receive [Lu-177]-PNT2002, along with reasons for screen failure, will be shown with percentages based on the Imaging Analysis Set. For the Randomized Treatment Phase, the subjects in the Imaging Analysis Set who were not randomized, along with reasons for not being randomized, will be shown with percentages based on the Imaging Analysis Set.

For the Dosimetry Phase, the number and percentage of subjects in the DAS will be displayed with the percentage based on the number in the Imaging Analysis Set. For the Randomized Treatment Phase, the number and percentage of subjects in the ITT Set will be displayed by treatment group with the percentages based on the number in the Imaging Analysis Set. The number and percentage of subjects randomized to Arm B who crossover to [Lu-177]-PNT2002 will also be presented. The number and percentage of subjects who complete treatment,

discontinue treatment (including reasons for treatment discontinuation), are ongoing in the study, complete the study, and early terminate from the study (including reasons for early termination) will be displayed for the DAS for the Dosimetry Phase and for the ITT Set for the Randomized Treatment Phase (by treatment group).

A by-subject listing of disposition information will be presented for the Dosimetry Phase and Randomized Treatment Phase. A separate by-subject listing of screen failures along with the reason for screen failure, will also be presented.

3.4.2 Protocol Deviations and Exclusions from the Per Protocol Analysis Set

Protocol deviations that would affect the evaluation of the efficacy and safety endpoints will be considered important protocol deviations. Important deviation includes but not limited to the following general categories:

- Subjects randomized but did not receive study treatment
- Subjects received randomized study treatment at an incorrect dose
- Missing baseline soft tissue or bone scan assessment
- Missing two or more consecutive soft tissue or bone scan assessment
- Use of prohibited concomitant medications

The categorization of important deviation will depend on duration and the perceived effect on efficacy and safety. Study clinical team and study statistician will review the protocol deviations and the final classification will be made prior to database lock and all decisions will be made blinded to subject identification.

All important protocol deviations will be shown in a subject listing for the Dosimetry Phase and for the Randomized Treatment Phase. For the Randomized Treatment Phase, subjects from the ITT Analysis Set who were excluded from the PPAS will be presented in a listing and also summarized in a table, showing reasons for exclusion and important deviations leading to exclusion.

3.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized separately for subjects in the Dosimetry Phase and Randomized Treatment Phase.

3.5.1 Demographics and Baseline Disease Characteristics

All demographic and baseline characteristics data will be summarized descriptively by treatment group and overall for the DAS and ITT.

Descriptive statistics will be displayed for age at consent, body mass index (BMI= weight in kg / (height in m)^2), baseline ALP, Lactate Dehydrogenase, Albumin/Serum Creatinine, renal impairment level and baseline PSA level. Frequencies and percentages will be tabulated for age groups (<65 years vs. >=65 years), race, ethnicity, country, ECOG performance status, and prior treatment/disease characteristic groups used as randomization strata in the Randomized Treatment Phase (both as randomized and as reported in the eCRF): prior taxane treatment in a

CSPC setting (yes or no), prior use of bisphosphonates (yes or no), metastatic status on prior ARAT (M0 or M1), and measurable disease at study entry (yes or no).

All demographics and baseline characteristics will be presented by subject in a data listing.

3.5.2 Prior Cancer Therapy and Cancer-Related Surgery

Prostate cancer history will be reported descriptively for the following characteristics:

- Time (months) from initial pathological diagnosis to study screening
- Gleason score at initial pathological diagnosis, and if Gleason score at initial pathological diagnosis is unknown
- Cancer staging:
    - primary tumor (T) stage
    - regional lymph nodes (N) stage
    - distant metastasis (M) stage
- Stage at initial diagnosis (I/IIA/IIB/IIC/IIIA/IIIB/IIIC/IVA/IVB)
- Time from mCRPC diagnosis to study screening (months)
- Metastatic disease site(s) at screening
- Progression criteria that subject met at screening:
    - serum PSA
    - soft-tissue progression (nodes)
    - soft-tissue progression (viscera)
    - bone progression
    - If progression was determined radiographically, type of radiographic progression:
        - appearance of new lesions
        - growth of existing lesions
        - both
- Time (months) from first progression on the last line of therapy to study screening

The number of months from initial pathological diagnosis and from first progression on the last line of therapy to study screening will be calculated relative to the month and year of the date of informed consent. When month is not reported for initial pathological diagnosis or first progression on the last line of therapy, then duration until screening will be calculated using years and then converted to months assuming 12 months in a year.

Prior systemic anticancer treatment will be summarized with frequencies and percentages for the following: prior progression on ARAT agents (prior enzalutamide vs. prior abiraterone vs. prior darolutamide vs. prior apalutamide), prior chemotherapy for HSPC (yes/no).

Subject frequencies and percentages will also be calculated for any prior radiotherapy (yes/no), radiation type, radiation intent, radiation treatment location, any prior prostate cancer-related surgery (yes/no), and surgical procedure name.

Prior cancer therapies and surgeries will be summarized by treatment group and overall for the DAS and ITT. By-subject listings will also be presented.

3.5.3 Medical/Surgical History

All medical/surgical history conditions will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 23.1) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Medical/surgical history will be tabulated by SOC and PT for each treatment group and overall for the DAS and ITT. All medical and surgical history conditions will be included in subject data listings.

3.6 Prior and Concomitant Medications/Procedures

Data from the following four eCRF pages will be summarized separately for subjects in the Dosimetry Phase and Randomized Treatment Phase:

- Prior and concomitant medications
- Opioids for prostate related cancer pain
- Non-cancer treatment procedures
- Cancer treatment procedures

Therapies (referring to medications or procedures) that occur before the administration of imaging agent are defined as Prior Therapies for imaging agent.

Therapies that are concomitant to study treatment will be determined separately from those that are concomitant to the imaging agent. Therapies that continue through the date of administration, started on or after the date of administration of the imaging agent (but not more than 7 days after administration of imaging agent) are defined as concomitant therapies for imaging agent. Therapies that continued or started on or after the 1st dose of randomized treatment but no more than 56 days after end of randomized treatment are defined as concomitant therapies for study treatment. Therapies that are ongoing on the date of the first administration of study drug will be classified as both prior and concomitant. Any therapy that cannot be confirmed as stopping before the start of study drug will be classified as both a prior and a concomitant therapy.

Partial medication dates will be imputed with maximum conservatism as described in Section 4.1.1 when determining if a therapy is concomitant. Imputed partial dates will only be used for identifying whether a medication was concomitant. Listings will display the partial dates as recorded on the eCRF.

All medications will be coded with the WHO Drug Dictionary (WHO-DD B3 format, Sept 2020). For medications that are concomitant to study treatment, the number and percentage of subjects in each treatment group and overall who took at least one medication as well as the number and percentage of subjects who took each type of medication will be summarized by Anatomical Therapeutic Chemical (ATC) Level 4 and PT. If a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a

subject has more than one PT within ATC Level 4, then the subject will be counted only once in that ATC Level 4 .

All procedures will be coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 23.1) and will be classified by MedDRA SOC and PT. Non-cancer treatment procedures and cancer treatment procedures will be tabulated separately by SOC and PT for each treatment group and overall. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject. Similarly, if a subject has occurrences of different PTs within an SOC, the subject will be counted only once in that SOC.

All medications prior to imaging agent, prior to study treatment, concomitant to imaging agent, and concomitant to the study treatment will be presented in listings. Procedures will be presented similarly.

3.7 Treatment Exposure and Compliance

Treatment exposure and compliance will be summarized separately for subjects in Dosimetry Phase and Randomized Treatment Phase.

3.7.1 Exposure to Study Treatment

The frequencies and percentages of the PSMA-PET imaging agents (^{68}Ga-PSMA-11 and ^{18}F-DCFPyL) used at screening will be reported for the Imaging Analysis Set. For the Dosimetry Phase, treatment exposure will be described using summary statistics for subjects in the DAS. For the Randomized Treatment Phase, treatment exposure will be summarized for the RSAS by study treatment using summary statistics. In this section, study treatment refers to [Lu-177]-PNT2002 for Arm A; abiraterone (with prednisone or dexamethasone) and enzalutamide for Arm B (which will be summarized separately); and [Lu-177]-PNT2002 for Arm B crossover subjects. Exposure to [Lu-177]-PNT2002 will be analyzed separately for Arm A and Arm B crossover subjects.

Exposure to study drugs in Arm B will be summarized by the duration of treatment in weeks and the cumulative dose received per subject, where treatment duration will be calculated as: ([last dose date - first dose date +1]/7).

Exposure to [Lu-177]-PNT2002 will be presented as the frequency and percentages of [Lu-177]-PNT2002 administrations per subject and as summary statistics of the number of cycles and doses per cycle of [Lu-177]-PNT2002 received per subject. The average dose of [Lu-177]-PNT2002 per subject per cycle and the cumulative dose of [Lu-177]-PNT2002 per subject across Arm A will also be summarized.

Additionally, the following will be presented, as applicable, with percentages: number of subjects with any [Lu-177]-PNT2002 dose modification with reasons for dose modification (e.g., adverse event, dosing error, or other); number of subjects with any control dose modification with reasons for dose modification (adverse event or other); type of [Lu-177]-PNT2002 dose modification (e.g., reduction, delay, or interruption); type of control dose modification (reduced or missed); number of subjects with any [Lu-177]-PNT2002 infusion-related reaction; and number and percentage of subjects with a [Lu-177]-PNT2002 dose reduction to 5GBq after the first dose (with percentage calculated based on the number of subjects with more than one dose of [Lu-177]-PNT2002). Post-treatment cancer-related therapy will be summarized as frequency

and percentages and be reported by treatment group.

All treatment exposure data will be presented in subject listings.

3.7.2 Compliance to Study Treatment

[Lu-177]-PNT2002 is administered under the supervision of the investigator or qualified designee. Compliance will be calculated as the percentage of received treatment doses out of the number of planned doses during the treatment period.

In Arm B of the Randomized Treatment Phase, study drug is self-administered per standard of care. Compliance will be calculated as the percentage of study drug (enzalutamide or abiraterone) doses actually taken out of the number of prescribed doses during the treatment duration.

Compliance rates will be presented for the DAS and RSAS by treatment group and for cross-over subjects using summary statistics. Individual subject compliance will be presented in a data listing.

3.8 Efficacy Analysis

Efficacy analyses will be conducted separately for subjects in the Dosimetry Phase and Randomized Treatment Phase. The same efficacy endpoints, described below, will be analyzed for both phases. Analyses for the Dosimetry Phase will be descriptive only. Inferential analyses described below apply to comparisons of Arm A and Arm B in the Randomized Treatment Phase. For the efficacy analysis comparisons, Arm B refers to the period of control treatment with abiraterone or enzalutamide, unless otherwise specified.

For the Randomized Treatment Phase, all efficacy analyses will be based on the ITT unless otherwise specified. Additionally, the analyses of the primary endpoint, rPFS by BICR and key secondary endpoints, OS and ORR, will be repeated on the PPAS as sensitivity analyses. Listings will be provided for primary efficacy endpoints.

3.8.1 Primary Efficacy Endpoint

Analysis of the primary endpoint, rPFS by BICR, will take place when CCI subjects experience radiological progression by BICR or die. The inferential comparison of the 2 randomized treatment groups with respect to rPFS by BICR will be made using a one-sided, stratified log-rank test with a significance level of CCI [redacted] If the one sided p-value is CCI the null hypothesis will be rejected with the conclusion that rPFS in the [Lu-177]-PNT2002 arm is statistically superior to that of the control arm (abiraterone or enzalutamide).

The hazard ratio for rPFS and the associated 95% CI will be estimated from a Cox proportional hazards model CCI [redacted]

The rPFS will also be descriptively analyzed using the Kaplan-Meier method. The median, and first and third quartiles with corresponding 95% CIs will be displayed. Summaries will include

the number at risk, the number of subjects with events, the number of subjects censored and their corresponding reason for censoring. Figures will use the Kaplan-Meier estimates and identify the number of subjects at risk over time and censored times on the curve.

Sensitivity analyses of rPFS

For all sensitivity analyses of rPFS, the number of subjects at risk and the number of subjects with events will be reported for each arm. The rPFS curve will be estimated using the Kaplan-Meier method. The median survival time and 95% CI along with rPFS at landmark timepoints, for instance, CCI [redacted] will be reported per arm. The hazard ratio and associated 95% CI, and the p-value will be estimated using the same methods as that used in the primary analysis.

Sensitivity analysis one: the primary analysis of rPFS will be repeated for the PPAS as a sensitivity analysis.

Sensitivity analysis two: as the primary analysis of rPFS will censor subjects at the last assessment prior to initiating a new anticancer therapy, to address the possible confounding of rPFS results, a sensitivity analysis will be conducted in which the subjects who receive a new anticancer therapy but have radiologic progression after initiation of that therapy will not be censored and will be counted as progressed at the time of progression following the new therapy, and the subjects who received the new anticancer therapy but did not progress will be censored at the last disease assessment regardless of the timing of the new anticancer therapy. All other censoring rules of the primary analysis of rPFS will be followed.

Sensitivity analysis three: in addition, a sensitivity analysis will be conducted counting start of anticancer treatment prior to radiological progression as an event. Hence, for this sensitivity analysis the rPFS time is defined as the time in months from the date of randomization to date of objective disease progression (soft tissue or bone), initiation of a new anticancer therapy, or death from any cause (whichever is earlier). All other censoring rules of the primary analysis of rPFS will be followed.

Sensitivity analysis four: the primary analysis of rPFS will also be repeated based on investigator-assessed tumor response as a sensitivity analysis.

Sensitivity analysis five: the primary analysis of rPFS will be repeated except rPFS will be defined from the date of first dose of randomized treatment. Subjects randomized who didn't receive study treatment will be censored to randomization date.

Sensitivity analysis six: the primary analysis of rPFS will be repeated except COVID-19 related deaths without progression will be censored at the last assessment prior to the death.

Subgroup analyses of rPFS

Subgroup analyses will be conducted for the primary endpoint rPFS by BICR CCI [redacted]
Values collected on the eCRF will be used to define subgroups for stratification factors. Additional subgroups of interest include:

- Lactate Dehydrogenase (<=260 IU/L vs. >260 IU/L)
- Age at informed consent (<65 vs. >= 65 years)

- Region (Europe vs. North America)
- Race (White, Black/African-American, Asian, Other)
- Baseline PSA score (below vs. equal to/above median baseline PSA across randomized arms)
- Opioid use at baseline (yes vs. no)
- Renal impairment status at baseline (eGFR [estimated Glomerular Filtration Rate] by Cockroft-Gault)
- Normal renal function (≥90 mL/min)
- Mild impairment (60-89 mL/min)
- Moderate impairment (30-59 mL/min)
- Severe impairment (15-29 mL/min)
- CCI [redacted]

Within each variable/factor of interest, the hazard ratio for rPFS and the associated 95% CI for each subgroup will be estimated from a Cox proportional hazards model including three covariates: the treatment group, the factor, and the treatment-by-factor term. The hazard ratio and 95% CI from the primary rPFS and each subgroup will be presented in a forest plot. No p-values will be calculated. Kaplan-Meier estimates will also be presented for each subset. If there are less than 5 events across the two arms or no events in either one of the arms for a subgroup, the hazard ratio will not be reported for that subgroup.

The same subgroup analyses will be performed for the rPFS by investigator assessment with the same analysis method and reported as described above. The Opioids for Prostate Related Cancer Pain form will be used in deriving Opioid use at baseline.

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3.8.2 Key Secondary Efficacy Endpoints

For time-to-event secondary efficacy endpoints, such as overall survival, time to opioid use, time to pain progression, time to second progression or death, the inferential comparison of the 2 randomized treatment groups will be made using the same method as that used for the primary endpoint. Specifically, p-value from stratified log-rank tests and the hazard ratio and the associated 95% CI from stratified Cox proportional hazard models will be reported. CCI [redacted]

3.8.2.1 Overall Survival (OS)

If the boundary is crossed for the primary rPFS analysis, the inferential comparison of the 2 randomized treatment groups with respect to OS will be made using a one-sided, stratified log-rank test with a significance level of CCI The strata used for the test will be the same strata used for the primary endpoint rPFS analysis. The interpolated spending function will be used to control an overall alpha of CCI

If the p-value for the stratified log-rank test of OS is CCI the null hypothesis will be rejected with the conclusion that OS in the [Lu-177]-PNT2002 arm is statistically superior to that of the control arm. CCI

Kaplan-Meier estimates and 95% CIs will be reported for median OS time and also OS landmark at timepoints of CCI OS summaries will include the number of subjects at risk, the number of subjects who died, and the number of censored subjects. The hazard ratio for OS and the associated 95% CI will be estimated from the Cox proportional hazards model used for the primary rPFS analysis.

In addition, the survival follow-up, defined as the duration between the reference date and the last known alive date/death date, in months, will be analyzed by the reverse Kaplan-Meier (i.e., with censoring at date of death for those who died). The median follow-up time and its corresponding 95% CI will be summarized. For the Randomized Treatment Phase, the reference date is the randomization date. For the Dosimetry Phase, the reference date is the enrollment date.

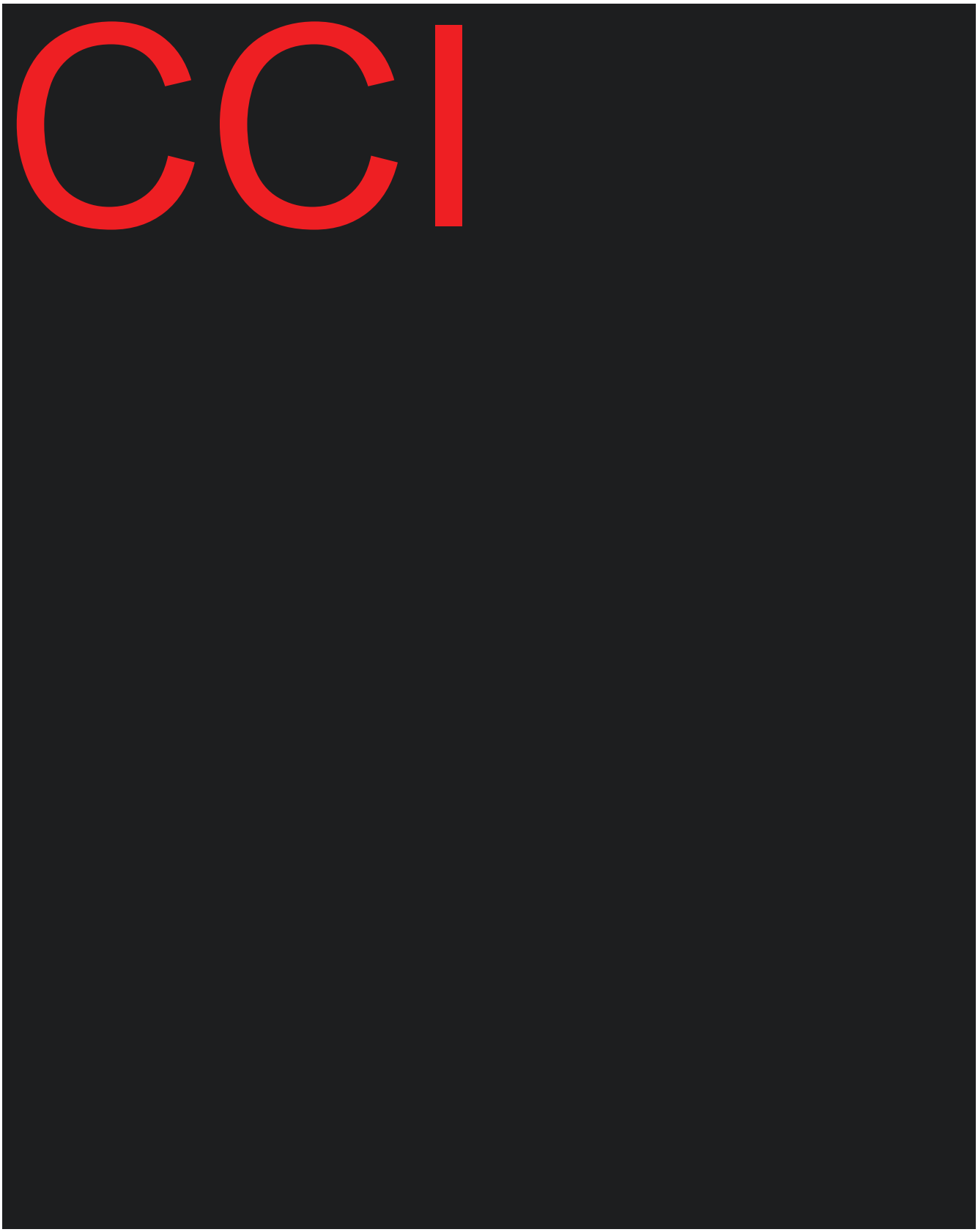
Sensitivity analyses of OS

To explore the impact of crossover from control arm to [Lu-177]-PNT2002 on OS, switching adjusted OS analysis has been generated using the Rank Preserving Structural Failure Time Models (RPSFTM)CCI

CCI

Rank Preserving Structural Failure Time Models

Sensitivity analyses one and two: To adjust for the confounding effects of the crossover from the control arm to [Lu-177]-PNT2002, RPSFTM will be used. Two analyses will be performed, first a continuing treatment effect will be assumed (subjects that switch are evaluated as "on treatment" from the time of switch until death), with re-censoring at data cut-off date for the control arm subjects that crossed-over to [Lu-177]-PNT2002 and did not have an event. The second sensitivity analysis will assume subjects who switch only receive benefit for the time they are receiving [Lu-177]-PNT2002. (i.e., assuming no benefit of [Lu-177]-PNT2002 from end of [Lu-177]-PNT2002 treatment until death for subjects that crossed-over). In both sensitivity analyses, subjects randomized to the [Lu-177]-PNT2002 arm will be considered "on treatment" from randomization until death. The second sensitivity analysis will result in a more conservative adjustment for the crossover effect.



Subgroup analysis of OS

Subgroup analyses specified for the primary endpoint rPFS will be conducted for OS CCI [redacted] Values reported in the eCRF will be used to define subgroups for stratification factors. For the subgroup analysis, the OS hazard ratio for each subgroup and the associated 95% CI will be estimated using the same method as in the rPFS subgroup analyses. The hazard ratio and 95% CI for the primary OS and all subgroups will be presented in a forest plot. No p-values will be calculated. Kaplan-Meier estimates will also be presented for each subset. If there are less than 5 events across the two arms or no events in either one of the arms for a subgroup, the hazard ratio will not be reported for that subgroup.

3.8.2.2 Objective Response Rate (ORR)

The primary analysis of ORR is the confirmed ORR assessed by BICR out of all subjects with measurable disease (target lesion) at baseline. For each treatment group the ORR and the corresponding 95% CIs will be provided. The ORR will be compared between treatment arms

using a logistic regression model with treatment group as the only covariate in the model and stratified by the stratification factors used in primary endpoint rPFS models. The results of the analysis will be presented by odds ratio (active:control) together with its associated Wald CI and two-sided p-value, with an odds ratio greater than 1 favoring the [Lu-177]-PNT2002 arm.

Best objective response (BOR) based on BICR assessment will also be reported descriptively out of all subjects with measurable disease at baseline. For each treatment group BOR will be summarized by number and percentage for each category (CR, PR, SD, PD and NE). For subjects with a BOR of SD, the number and the percentage of subjects who had an unconfirmed response of CR/PR will be displayed.

Sensitivity analysis of ORR

In addition to the primary analysis, the below sensitivity analyses will also be conducted for different assessments (BICR vs. investigator), whether requiring response confirmed (confirmed ORR vs. ORR), and different population set (measurable [target lesion] vs. evaluable set [target and/or non-target lesion]).

Sensitivity analysis one: ORR by BICR (without requiring response to be confirmed) among all subjects with measurable disease at baseline.

Sensitivity analysis two: Confirmed ORR by BICR among all subjects with evaluable disease at baseline, i.e., subjects with either measurable or non-measurable disease at baseline.

Sensitivity analysis three: ORR by BICR among all subjects with evaluable disease at baseline.

Sensitivity analysis four: Confirmed ORR by investigator among all subjects with measurable disease at baseline.

Sensitivity analysis five: ORR by investigator among all subjects with measurable disease at baseline.

Sensitivity analysis six: Confirmed ORR by investigator among all subjects with evaluable disease at baseline.

Sensitivity analysis seven: ORR by investigator among all subjects with evaluable disease at baseline.

Sensitivity analysis eight: the main analysis of ORR will be repeated for the PPAS as a sensitivity analysis.

Sensitivity analysis nine: a sensitivity analysis using a Chi-square test for 2 proportions (not stratified) will be performed.

Sensitivity analysis ten: The “best case scenario” sensitivity analysis will also be performed with the subjects who do not have any tumor response prior to discontinuation counted as responders, versus the main ORR analysis with these subjects counted as non-responders.

3.8.2.3 Time to First Symptomatic Skeletal-Related Event (SSRE)

Kaplan-Meier estimates will be produced for time to first SSRE, as defined in Section 2.2.4.4, by randomized treatment group. Summaries will include the number of subjects at risk, the number of subjects with SSREs, and the number of censored subjects. The KM estimate of the median SSRE event free survival time with corresponding 95% CIs, landmark estimate of SSRE event

free rate at CCI will be reported within each treatment group. The hazard ratio and the associated 95% CI will be estimated using the same Cox proportional hazards model as used in the primary rPFS analysis. The 2-sided p-value will be calculated using the same stratified log-rank test as in the primary rPFS analysis.

3.8.3 Secondary Efficacy Endpoints

3.8.3.1 Duration of Response

Kaplan-Meier estimates will be produced for DOR for responders by randomized treatment group. Summaries will include the number of subjects at risk, the number of subjects with events, and the number of censored subjects. The KM estimate of the median DOR time with corresponding 95% CIs will be reported within each treatment group. DoR will be calculated for confirmed response or response without confirmation, response assessed by BICR or by investigator, within measurable disease or evaluable disease sets separately.

3.8.3.2 PSA Response Rate

The number and percentage of subjects with PSA response (confirmed or unconfirmed) will be presented by treatment group. For each treatment group, the PSA response rate (confirmed or unconfirmed) and the corresponding 95% CIs will be provided. For PSA response comparison, analyses will be the same as those described for binary outcome ORR. Summary statistics of best % change from baseline and waterfall plot of the maximum % change from baseline in PSA for each subject will be produced.

3.8.3.3 Biochemical Progression-Free Survival

Kaplan-Meier estimates will be produced for bPFS by randomized treatment group. Summaries will include the number of subjects at risk, the number of subjects with biochemical progression, and the number of censored subjects. The KM estimate of the median bPFS time and the corresponding 95% CIs will be reported within each treatment group. The hazard ratio and the associated 95% CI will be estimated using the same Cox proportional hazards model as used in the primary rPFS analysis.

3.8.3.4 Concordance between BICR and Investigator Assessments

Concordance between BICR and investigator assessments will be reported for rPFS. Concordance will be summarized by concordance status and type of concordance (concordant rPFS event vs. concordant no rPFS event) within each treatment group and overall. For concordant rPFS event, timing and type of progression event (RECIST progression only vs. Bone progression only vs. RECIST and Bone progression) will also be reported.

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3.9 Safety Analysis

Safety analyses will be conducted separately for subjects in the Dosimetry Phase and Randomized Treatment Phase. Safety analyses will be based on the DAS and RSAS. Descriptive statistics will be used to summarize all safety endpoints by treatment group.

For imaging agent, the period that is emergent to the imaging agent will be defined as the period from the date of imaging agent dosing up to [redacted] days post imaging agent administration but before the date of 1st dose of study treatment.

For study treatment, the treatment-emergent period will be defined as the period from the date of 1st dose of study treatment, up to CCI [redacted] after the date of the last administration of study treatment for subjects that have ended treatment, or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first. For Arm B subjects who crossover upon BICR PD, the [Lu-177]-PNT2002 treatment emergent period will be defined as the period from

the date of 1st dose of [Lu-177]-PNT2002, up to CCI after the date of the last dose for subjects that have ended treatment, or the day prior to the initiation of other subsequent anticancer treatment, whichever occurs first.

For subjects who received imaging agent only, incidence of adverse events that are emergent to the imaging agent will be reported. For subjects who received both imaging agent and study treatment, data summaries will be displayed for incidence of TEAEs, incidence of death, AE of special interest, clinical laboratory variables, ECGs, and vital signs. All safety data summaries will be repeated for Arm B subjects who crossover and received [Lu-177]-PNT2002.

All scheduled and unscheduled data will be included in outputs that summarize values by visits with the exception of ECGs. Since ECGs are collected pre-dose and 4 hours post-dose on each dosing visit, they will by summarized by the reported visit to maintain the timing with the respect to the dosing. Time windows for the visits post baseline will be centered at the scheduled day of the visit, and the upper limit of the interval falls half way between the two consecutive visits. The lower limit of the first post-baseline visit will be day 1 after the first dose. If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. For example for Arm A subjects, safety assessment scheduled every 2 weeks such as blood chemistry, hematology, and vital signs will be windowed as:

- Week 2 visit (day 15), visit window: day 1 – day 21
- Week 4 visit (day 29), visit window: day 22 – day 35
- Week 6 visit (day 43), visit window: day 36 – day 49

For Arm A and Arm B, safety assessment scheduled every 4 weeks will be windowed as:

- Week 4 visit (day 29), visit window: day 1 – day 42
- Week 8 visit (day 57), visit window: day 43 – day 70
- Week 12 visit (day 85), visit window: day 71 – day 98

Time windows will be exhaustive such that all post-baseline data collected will be included in a visit window. Time window assigning will be based on the actual visit date not the planned date of visits. For summaries at a subject level, all values will be used in deriving a statistics, for instance, minimum or maximum, regardless of which time window it falls or scheduled or not. For summaries at a visit level, if there are multiple values per subject collected within a time window, then the closest value to the scheduled visit date will be used. If there are two or more values recorded on the same day and the parameter is CTCAE gradable, then the record with the highest toxicity grade will be used. If the parameter is not CTCAE gradable, then the record on that day with the largest absolute change from baseline will be used or largest value if change from baseline is not defined.

3.9.1 Adverse Events

All adverse events will be coded using the MedDRA Version 23.1 and will be classified by MedDRA SOC and PT.

All SAEs will be collected from date of signed informed consent through the EOT/Safety Follow-Up Visit (i.e., 8 weeks after last dose of study treatment). All AEs will be collected from first dose of Investigational Product (i.e., PSMA imaging agent) through the EOT Visit. AEs will be assigned as emergent to the imaging agent, [Lu-177]-PNT2002 treatment-emergent or

abiraterone or enzalutamide treatment-emergent based on which period AEs occurred. Subjects that cross over from Arm B to receive [Lu-177]-PNT2002 may have treatment-emergent AEs under both treatments.

For all summaries, SOCs and PTs within SOC will be presented by decreasing frequency of incidence (with grades combined, if applicable), sorted first for Arm A ([Lu-177]-PNT2002 arm) and then for Arm B (abiraterone or enzalutamide).

Rules for handling incomplete or missing adverse event start dates are addressed in Section 4.1.2 (stop dates will not be imputed). The imputation of dates will be used to decide if an adverse event is treatment-emergent only. The imputed dates will not be used to calculate durations. Where partial dates occur, listings will contain the date collected in the partial form.

3.9.1.1 Overall Summary of AEs

An overall summary of TEAEs will be presented by treatment group. The number and percentage of subjects who experienced any TEAE, any treatment-related TEAE, any TEAE of CTCAE Grade 3 or above, any treatment-related TEAE of CTCAE Grade 3 or above, any serious TEAE, any treatment-related serious TEAE, any TEAE of special interest, any TEAE leading to treatment interruption, any treatment-related TEAE leading to treatment interruption, any TEAE leading to treatment delay, any treatment-related TEAE leading to treatment delay, any TEAE leading to treatment dose reduction, any treatment-related TEAE leading to treatment dose reduction, any TEAE leading to treatment discontinuation, any treatment-related TEAE leading to treatment discontinuation, any TEAE leading to death, and any treatment-related TEAE leading to death will be displayed. Treatment-related TEAEs are events with a study treatment causality of ‘possible’, ‘probable’, ‘definite’, or missing.

3.9.1.2 AE Incidences

The incidence of TEAEs will be presented by treatment group. The number and percentage of subjects who experienced any TEAE as well as the number and percentage of subjects who experienced each specific SOC and PT will be presented. For this analysis, if a subject has more than one occurrence of the same PT, then the subject will be counted only once in that PT. If a subject has occurrences of different PTs within an SOC, the subject will be counted once in each PT but only once in that SOC. If a subject has occurrences of different PTs across different SOCs, then the subject will be counted once in each of those PTs and once in each of those SOCs.

The number and percentage of subjects who experienced any TEAE as well as the number and percentage of subjects who experienced each specific SOC and PT will also be presented by maximum CTCAE grade. For this analysis, a subject is counted once per each PT within a SOC under the worst (maximum) grade. A summary table by PT and maximum CTCAE grade will also be presented. For this analysis, a subject is counted once per each PT under the worst (maximum) grade.

A summary table of AE incidences by PT only will also be presented, sorted by decreasing PT incidence (in Arm A then Arm B for Randomized Treatment Phase). Additionally, the most common (>=5% overall incidence) TEAEs by PT will be summarized. All COVID-19 related AEs will also be summarized. TEAEs of CTCAE Grade 3 or above will be presented by SOC and PT. TEAEs by SOC, PT, and maximum relationship will be summarized.

All TEAEs will be included in a subject listing. Additionally, listings will be produced for deaths (with AEs leading to death indicated), serious AEs (with drug-relatedness indicated), AEs that led to study drug withdrawal, and AEs of special interest.

For AEs emergent to the PSMA imaging agent only, a separate listing will also be produced based on the Imaging Analysis Set, with the Dosimetry Phase and Randomized Treatment Phase combined. A list of all AEs that are not emergent but has been identified as related to imaging agent will also be generated for all subjects who received imaging agent.

3.9.1.3 Serious AEs

A summary of serious AEs will be presented by SOC, PT, and maximum reported CTCAE grade by treatment group. A subject will be counted once per each PT within a SOC under the worst (maximum) grade. Based on the Imaging Analysis Set, a listing will be produced for all SAEs.

3.9.1.4 Deaths

Based on the Imaging Analysis Set, a listing and summary will be produced for all deaths.

3.9.1.5 Related AEs

Adverse event relationship to study treatment as well as relationship to imaging agent are collected. The incidence of any drug-related TEAEs (either study treatment or imaging agent) will be presented within SOC and PT by treatment group. Additionally, the incidence of any related TEAEs will be presented separately for study treatment and imaging agent within SOC and PT by treatment group. Related TEAEs will be defined as those with a ‘possible’, ‘probable’ or ‘definite’ relationship to treatment/imaging agent. TEAEs with missing relationship will be counted as related. For this analysis, if a subject has more than one occurrence of the same PT, then the subject will be counted only once in that PT. If a subject has occurrences of different PTs within an SOC, the subject will be counted once in each PT but only once in that SOC. If a subject has occurrences of different PTs across different SOCs, then the subject will be counted once in each of those PTs and once in each of those SOCs.

A similar table of any drug-related (either study treatment or imaging agent) serious AEs will be created. Any drug-related TEAEs (either study treatment or imaging agent) by SOC, PT, and maximum reported CTCAE grade will also be presented by treatment group.

3.9.1.6 AEs Leading to Study Treatment Discontinuation, Reduction, Interruption, or Delay

A summary of TEAEs that led to study treatment discontinuation, reduction, interruption, or delay will be presented within SOC, PT, and maximum CTCAE grade by treatment group. A subject is counted once per each PT.

3.9.1.7 AEs of Special Interest

The following late-stage radiation toxicities are considered adverse events of special interest (AESIs) when they occur at least 12 months from the first dose of [Lu-177]-PNT2002 and when deemed causally related to [Lu-177]-PNT2002:

- Xerostomia or dry mouth

- Xerophthalmia or dry eye disorders related to radiation exposure
- Renal dysfunction
- Creatinine increase
- Acute kidney injury
- Secondary malignancies

All AEs of special interest will be identified by the investigator and reported on the eCRF. AESI will be reported 12 months from 1st dose of study treatment until end of Long-term Follow Up. The number and percentage of subjects who experienced each AE of special interest will be presented. For this analysis, if a subject has more than one occurrence of the same AE of special interest, then the AE will be counted only once for that subject (e.g., subject incidence).

3.9.2 Clinical Laboratory Evaluation

Continuous hematology and chemistry laboratory data will be examined for trends using descriptive statistics (n, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum) of observed values and changes from baseline to each planned post-baseline visit.

Additionally, for those hematology and chemistry laboratory parameters where CTCAE grading is applicable, values will be categorized according to CTCAE version 5.0. Clinical symptoms and interventions which are included in the CTCAE grade definitions will not be considered in grading shifts. Only reported numerical lab values will be utilized. CTCAE terms will be used to describe toxicity events. If toxicity can be experienced at both low and high values for a parameter, then toxicity grade for low values will be defined separately from toxicity grade for high values. Frequencies and percentages will be shown for the shifts from baseline CTCAE grade to the worst post-baseline grade. For CTCAE events where baseline grade cannot be defined, baseline lab values will be categorized as <= upper limit of normal versus > upper limit of normal; this applies to the following CTCAE events: alanine aminotransferase increased, aspartate aminotransferase increased, alkaline phosphatase increased, and blood bilirubin increased.

The following hematology and chemistry parameters will be summarized (with CTCAE toxicity events described in parentheses):

Hematology:

- Basophils
- Basophils (abs.)
- Eosinophils
- Eosinophils (abs.)
- Hematocrit
- Hemoglobin (with CTCAE terms: hemoglobin increased and anemia)
- Lymphocytes
- Lymphocytes (abs.) (with CTCAE terms: lymphocyte count increased and decreased)

- MCH
- Mean Corpuscular Volume
- Monocytes
- Monocytes (abs.)
- Neutrophils
- Neutrophils (abs.) (with CTCAE term: neutrophil count decreased)
- Platelet Count (with CTCAE term: platelet count decreased)
- RBC Count
- WBC Count (with CTCAE terms: leukocytosis and white blood cell decreased)

Chemistry:

- Albumin (with CTCAE term: hypoalbuminemia)
- Alkaline phosphatase (with CTCAE term: alkaline phosphatase increased)
- ALT (with CTCAE term: alanine aminotransferase increased)
- AST (with CTCAE term: aspartate aminotransferase increased)
- Bicarbonate
- Calcium
- Chloride
- Creatine Kinase (with CTCAE term: creatine phosphokinase increased)
- Glucose (non-fasting) (with CTCAE term: hypoglycemia)
- Lactate Dehydrogenase
- Magnesium (with CTCAE terms: hypermagnesemia and hypomagnesemia)
- Phosphate
- Potassium (with CTCAE terms: hyperkalemia and hypokalemia)
- Serum Creatinine (with CTCAE term: creatinine increased)
- Sodium (with CTCAE terms: hypernatremia and hyponatremia)
- Total Bilirubin (with CTCAE term: blood bilirubin increased)
- Total Protein
- eGFR [CKD-EPI] (with CTCAE term: chronic kidney disease)

The analyses will be performed using the DAS and RSAS and presented by treatment group.

In addition to listings for all laboratory parameter values, separate listings for PSA values, and all clinically significant laboratory abnormalities will be provided. Worst post-baseline abnormalities based on CTCAE Grade will be reported. Also, box plots will be created for

hematology, and chemistry values across visits for the RSAS by treatment group. Plots of ALT and AST vs. Total Bilirubin (TBL) expressed as multiples of Upper Limit Normal (ULN) will be created to identify Potential Hy's Law Cases.

3.9.3 ECG

ECGs will be performed at the Baseline visit, weeks 8, 16, 24 and EOT/Safety Follow-Up Visit (i.e., 8 weeks after last dose of study treatment) for subjects taking [Lu-177]-PNT2002 (except for those who cross over from Arm B control treatment to [Lu-177]-PNT2002). At Baseline and the Week 8, 16, and 24 visits, ECGs will be performed pre-dose and up to 4 hours post-dose. Descriptive statistics will be presented for ventricular heart rate, RR interval, PR interval, QRS duration, QT interval, and QTcF interval values at pre and post-dose by visit. For each parameter, descriptive statistics on the change from pre to post-dose will also be presented. Descriptive statistics will also be presented for the EOT visit assessments and the changes from baseline (pre-dose) to EOT.

These data will also be categorized by the investigator as normal, abnormal not clinically significant, and abnormal clinically significant. Frequencies and percentages will be shown for the shifts in these categories from pre-dose to post-dose at each dosing visit and from baseline (pre-dose) to the EOT visit.

A shift table for QTcF results will present the shift from baseline to worst post-baseline value (including unscheduled assessments) in the following categories:

- <=450 ms
- >450 to <=480 ms
- >480 to <=500 ms
- >500 ms
- Change from baseline >30 to <=60 ms
- Change from baseline >60 ms

All ECG results will be included in a subject listing.

3.9.4 Vital Signs and Other Physical Findings

Vital signs (temperature, pulse, respiratory rate, and systolic and diastolic blood pressure), weight, and BMI will be summarized descriptively at baseline and all post-baseline study visits by treatment group.

All vital sign results will be included in a subject listing.

3.9.5 Physical Examination

Any clinically significant or worsening abnormalities noted during physical examinations were recorded on the Medical History or Adverse Events forms.

3.10 Exploratory Endpoints

3.13 Changes to Analysis from Protocol

For the analysis of ORR (Section 3.8.2.2) and PSA response rate (Section 3.8.3.2), the response rates will be compared between treatment arms using a logistic regression model, stratified by the stratification factors used in primary endpoint rPFS models. The results of the analysis will be presented by odds ratio together with its associated profile likelihood CI and p-value, with an odds ratio greater than 1 favoring the [Lu-177]-PNT2002 arm. The protocol specified that the treatment group difference for ORR with the associated 95% CI and the p-value from a stratified Cochran-Mantel-Haenszel (CMH) test will be displayed. The change in the method is to better align with how the analyses were performed in similar studies such as the VISION trial for lutetium-177-PSMA-617.

4 DATA HANDLING

4.1 Date Imputation Rules

In the unusual case that the month portion of a date is missing but the day portion is not missing, the day portion will be assumed to be missing. Likewise, in the case where the year portion of a date is missing but the month and/or day portion is not missing, the month and/or day portion will be assumed to be missing.

4.1.1 Date Imputation for Medications

Rules for handling incomplete or missing medication start and end dates are addressed below.

All missing portion(s) of medication dates will be handled using the following rules:

- In the event that the day portion (and only the day portion) of the date is missing:
    - If the medication started in the same month and year as the first study treatment dose date, the medication start date will be assumed to be the first study treatment dose date.
    - Else if the medication started in the month before study treatment or earlier, and it started in the same month and year as the first dose date of PSMA imaging agent, then the medication start date will be assumed to be the first dose date of PSMA imaging agent.
    - Otherwise, the medication start date will be assumed to be the first day of the given month and year, e.g., XX–JAN-2005 would be 01-JAN-2005 where XX represents an unknown day.
    - The medication end date will be assumed to be the last day of the given month and year, e.g., XX–JAN-2005 would be 31-JAN-2005 where XX represents an unknown day.
- In the event that the day and month portions (and only the day and month portions) of the date are missing:

  - If the medication started in the same year as the first study treatment dose date, the medication start date will be assumed to be the first study treatment dose date.
  - Else if the medication started in the year before study treatment, and it started in the same year as the first dose date of PSMA imaging agent, then the medication start date will be assumed to be the first dose date of PSMA imaging agent.
  - Otherwise, the medication start date will be assumed to be first month and day of the given year, e.g., XX–XXX-2005 would be 01-JAN-2005 where XX represents an unknown day and XXX represents an unknown month.
  - The medication end date will be assumed to be the last day of the given year, e.g., XX–XXX-2005 would be 31-DEC-2005 where XX represents an unknown day and XXX represents an unknown month.

- In the event that the day, month, and year portions of the medication start date are missing, it will be assumed to be the first study treatment dose date.
- In the event that day, month, and year portions of the medication end date are missing, it will be assumed to be the later of the medication start date and the first treatment dose date.

If imputation of a start date (and end date if both were imputed) results in a start date occurring after the end date, the imputed start date will be reset to equal the end date. If an imputed start or end date occurs after the database cut-off/lock date, the imputed date will be reset to the database cut-off/lock date.

4.1.2 Date Imputation for Adverse Events

Rules for handling incomplete or missing adverse event start dates are addressed below (stop dates will not be imputed).

All missing portion(s) of the date will be handled using the same rules:

- In the event that the day portion (and only the day portion) of the date is missing:
  - If the adverse event started in the same month and year as the first study treatment dose date, the adverse event start date will be assumed to be the first study treatment dose date.
  - Else if the adverse event started in the month before study treatment or earlier, and it started in the same month and year as the first dose date of PSMA imaging agent, then the adverse event start date will be assumed to be the first dose date of PSMA imaging agent.
  - Otherwise, the adverse event start date will be assumed to be the first day of the given month and year, e.g., XX–JAN-2005 would be 01-JAN-2005, where XX represents an unknown day.
- In the event that the day and month portions (and only the day and month portions) of the date are missing:

  - If the adverse event started in the same year as the first study treatment dose date, the adverse event start date will be assumed to be the first study treatment dose date.
  - Else if the adverse event started in the year before study treatment, and it started in the same year as the first dose date of PSMA imaging agent, then the adverse event start date will be assumed to be the first dose date of PSMA imaging agent.
  - Otherwise, the adverse event start date will be assumed to be first month and day of the given year, e.g., XX–XXX-2005 would be 01-JAN-2005, where XX represents an unknown day and XXX represents an unknown month.

- In the event that the day, month, and year portions of the adverse event start date are missing, it will be assumed to be the first study treatment dose date.

If the adverse event start date has been imputed using the rules above, then the adverse event start date must be compared with the adverse event stop date to ensure the logical ordering of dates. If the imputed adverse event start date is after the non-missing adverse event stop date, then the imputed start date will be reset as the stop date. If an imputed start date occurs after the database cut-off/lock date, the imputed date will be reset to the database cut-off/lock date.

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