^{64}Cu-SAR-BBN Positron Emission Tomography: A Phase 2 Study of Participants with PSMA-negative Biochemical Recurrence of Prostate Cancer

Protocol: CLB03

STATISTICAL ANALYSIS PLAN

Version 1.0

September 6, 2024

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STATISTICAL ANALYSIS PLAN

Protocol Title:	^{64}Cu-SAR-BBN Positron Emission Tomography: A Phase 2 Study of Participants with PSMA-negative Biochemical Recurrence of Prostate Cancer
Protocol Number:	CLB03
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Confidentiality Statement

SIGNATURE PAGE

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We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature	Date
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VERSION HISTORY

Version	Version Date	Description
1.0	06 September 2024	Original Signed Version

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation/Term	Definition
^{64}Cu-SAR-BBN	Copper-64-labeled SAR-BBN
ADaM	Analysis Data Model
ADL	Activities of Daily Living
ADT	Androgen-Deprivation Therapy
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CDR	Correct Detection Rate
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DR	Detection Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	False Positive
FPR	Rate of False Positive
GRPR	Gastrin Releasing Peptide Receptor
ICH	International Council for Harmonisation
ICF	Informed Consent Form

LLN	Lower Limit of Normal
ISO	International Organization for Standardization
IV	Intravenous
MBq	Mega Becquerel
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PT	Prothrombin Time
PC	Prostate Cancer
PET	Positron Emission Tomography
PP	Per Protocol
PPV	Positive Predictive Value
PSA	Prostate-Specific Antigen
PSADT	PSA Doubling Time
PSMA	Prostate Specific Membrane Antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	Standard of Care
SUV	Standardized Uptake Value
SUVr	Ratio of Standardized Uptake Value
TEAE	Treatment-Emergent Adverse Event
TN	True Negative
TNR	Rate of True Negative
TP	True Positive
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from the study with protocol number CLB03 (Version 2.0, 27 February 2023). If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report (CSR).

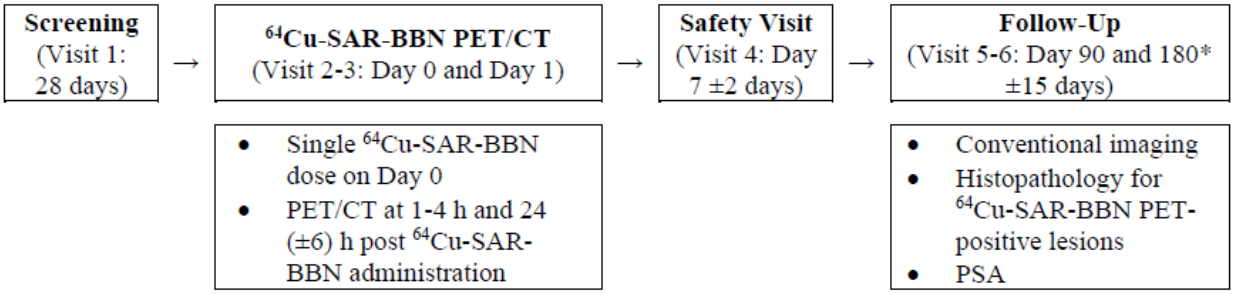
2 STUDY DESIGN

This is a phase 2, multi-center, single arm, non-randomized, open-label study of copper-64-labeled SAR-BBN (^{64}Cu-SAR-BBN) administered to participants with biochemical recurrence of prostate cancer (PC) following definitive therapy. Participants who provide informed consent will undertake a screening visit(s) to determine their eligibility to participate in the study. After the Screening period, eligible participants will receive a single administration of ^{64}Cu-SAR-BBN on Day 0, followed by a PET/CT scan at 1 to 4 hours post dose (Day 0 scan) and at 24 hours post dose (Day 1 scan). Safety of ^{64}Cu-SAR-BBN will be assessed post dose, on Day 0, Day 1 and Day 7. Participants will then continue into the Follow-up period to verify the ^{64}Cu-SAR-BBN PET/CT findings by histopathology, conventional imaging modalities that are routinely used in the diagnosis and staging of PC and prostate-specific antigen (PSA) levels.

The ^{64}Cu-SAR-BBN PET/CT scans will be interpreted by an appropriately qualified local Investigator and three independent, blinded central readers. The ^{64}Cu-SAR-BBN PET/CT findings will be assessed against a composite Reference Standard. The composite Reference Standard will be determined by an independent, blinded, central expert panel and may consist of histopathology, conventional imaging modalities that are routinely used in the diagnosis and staging of PC and PSA levels.

The overall study schema is presented in the Figure 1 Overall Study Design below, and the study procedures and assessments are detailed in Appendix A.

Figure 1 Overall Study Design



**Day 180 visit is only applicable for participants who were deemed negative or equivocal for PC recurrence at Day 90.*

Abbreviations: CT=computed tomography; h= hour; PET= positron emission tomography; PSA=prostate-specific antigen

3 INVESTIGATIONAL PRODUCT AND ADMINISTRATION

The investigational product administered in this study is ^{64}Cu-SAR-BBN. Clarity is developing this radiopharmaceutical for the diagnosis and management of Gastrin Releasing Peptide Receptor (GRPR)-positive tumors.

^{64}Cu-SAR-BBN has 3 basic components: the radionuclide (^{64}Cu), bound via MeCOSar (a bifunctional metal chelator) to an antagonist that targets GRPR. ^{64}Cu-SAR-BBN will be formulated as a sterile solution for IV injection suitable for human use. ^{64}Cu-SAR-BBN is considered an investigational product by the Food and Drug Administration (FDA), and as such will be under controlled conditions for use in clinical trials.

In this study, ^{64}Cu-SAR-BBN will be administered as a bolus IV injection single dose at a dosage of 200 MBq on Day 0.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Study Objectives and Endpoints

Objective	Endpoint
To investigate the safety and tolerability of ^{64}Cu-SAR-BBN.	Incidence and severity of treatment-emergent adverse events (TEAEs) and serious AEs (SAEs) following the administration of ^{64}Cu-SAR-BBN.
To investigate the ability of ^{64}Cu-SAR-BBN PET/CT to correctly detect recurrence of PC.	• Participant-level correct detection rate (CDR), defined as the proportion of true positive (TP) participants on the Day 0 scan out of all participants with a Day 0 scan. • Participant-level CDR, defined as the proportion of TP participants on the Day 1 scan out of all participants with a Day 1 scan.

Objective	Endpoint
	• Region-level positive predictive value (PPV), defined as the proportion of TP regions on the Day 0 scan out of all positive regions on the Day 0 scan. • Region-level PPV, defined as the proportion of TP regions on the Day 1 scan out of all positive regions on the Day 1 scan.

4.2 Secondary Study Objectives and Endpoints

Objective	Endpoint
To investigate the biodistribution of ^{64}Cu-SAR-BBN.	Biodistribution of ^{64}Cu-SAR-BBN on the Day 0 and Day 1 scan: • Maximum and mean standardized uptake values (SUVs) in lesion(s), visceral/soft tissue, bone. • Lesion-to-background ratio.
To assess the participant-level PPV of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level PPV, defined as the proportion of TP participants on the Day 0 scan out of all participants with a positive Day 0 scan. • Participant-level PPV, defined as the proportion of TP participants on the Day 1 scan out of all participants with a positive Day 1 scan.
To assess the participant-level detection rate (DR) of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level DR, defined as the proportion of participants with a positive Day 0 scan out of all participants with a Day 0 scan. • Participant-level DR, defined as the proportion of participants with a positive Day 1 scan out of all participants with a Day 1 scan.
To assess the rate of false positive (FPR) of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level FPR, defined as the proportion of false positive (FP) participants on the Day 0 scan out of all participants with a positive Day 0 scan. • Participant-level FPR, defined as the proportion of FP participants on the Day 1 scan out of all participants with a positive Day 1 scan. • Region-level FPR, defined as the proportion of FP regions on the Day 0 scan out of all positive regions on the Day 0 scan. • Region-level FPR, defined as the proportion of FP regions on the Day 1 scan out of all positive regions on the Day 1 scan.

Objective	Endpoint
To assess the discrepant PET negativity rate of the ^{64}Cu-SAR-BBN PET/CT scans.	Participant-level discrepant PET negativity rate, defined as the proportion of participants with contradicting Day 0 and Day 1 results for whom the Reference Standard was positive.
To assess the rate of true negative (TNR) of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level TNR, defined as the proportion of true negative (TN) participants on the Day 0 scan out of all participants with a negative Day 0 scan. • Participant-level TNR, defined as the proportion of TN participants on the Day 1 scan out of all participants with a negative Day 1 scan. • Region-level TNR, defined as the proportion of TN regions on the Day 0 scan out of all negative regions on the Day 0 scan. • Region-level TNR, defined as the proportion of TN regions on the Day 1 scan out of all negative regions on the Day 1 scan.

4.3 Exploratory Study Objectives and Endpoints

Objective	Endpoint
To evaluate the reproducibility of the ^{64}Cu-SAR-BBN PET/CT readings and consistency among readers.	• Intra-reader variability per reader. • Inter-reader variability expressed by kappa statistics.
To assess the impact of ^{64}Cu-SAR-BBN PET/CT on disease management.	Proportion of participants with any change in intended PC treatment due to either the Day 0 or Day 1 scan.
Composite performance of the Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT scans.	• Composite CDR defined as the proportion of TP participants on the Day 0 and/or Day 1 scan out of all participants with a Day 0 and/or Day 1 scan. • Composite participant/region-level PPV defined as the proportion of TP participants/regions on the Day 0 and/or Day 1 scan out of all participants/regions with a positive Day 0 and/or Day 1 scan. • Composite DR defined as the proportion of participants with a positive Day 0 and/or Day 1 scan out of all participants with a Day 0 and/or Day 1 scan.
To determine the effect of baseline variables on the CDR,	CDR, participant- and region-level PPV and DR of the Day 0 and/or Day 1 scan as a function of baseline variables.

Objective	Endpoint
PPV and DR of ^{64}Cu-SAR-BBN PET/CT.	
To explore the correlation between ^{64}Cu-SAR-BBN PET-positivity and Reference Standard results.	Relationship between PET-positivity (biodistribution measures such as SUVs and lesion-to-background ratio), versus true/false positivity and as a function of lesion location and size.
To assess the lesion-level performance of ^{64}Cu-SAR-BBN PET/CT.	• Difference in the number of lesions detected per participant on the Day 0 versus the Day 1 scan. • Overall agreement rate on the Day 0 and Day 1 scans, defined as the number lesions with matching subregion divided by the total number of lesions identified across all scans by either imaging. • Overall agreement rate on the Day 0 and reference scans, defined as the number lesions with matching subregion divided by the total number of lesions identified across all scans by either imaging. • Overall agreement rate on the Day 1 and reference scans, defined as the number lesions with matching subregion divided by the total number of lesions identified across all scans by either imaging.

5 HYPOTHESIS TEST AND SAMPLE SIZE EETIMATION

5.1 Hypothesis Test

There is no formal hypothesis testing planned in this study. All statistical testing and associated *p*-values are presented without controlling for the alpha level.

5.2 Sample Size Estimation

The co-primary endpoints include participant-level CDR or true positive detection rate and region-level PPV.

The assumed participant-level CDR of ^{64}Cu-SAR-BBN PET/CT imaging is 35% in participants with PSMA-negative biochemical recurrence of PC. A sample size of 40 participants is estimated to provide more than 80% power to achieve a lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated CDR that exceeds 15%. Accounting for a 20% non-evaluable rate (including lost to follow up), approximately 50 participants will need to undergo ^{64}Cu-SAR-BBN PET/CT in this study.

For the co-primary efficacy endpoint of region-level PPV, assuming 60% of participants are estimated to have ^{64}Cu-SAR-BBN PET/CT positive findings in this target population and each participant with positive findings has an average of 1.3 positive regions, then 40 participants are expected to produce approximately 31 positive regions. The assumed region-level PPV rate of ^{64}Cu-SAR-BBN PET/CT imaging is approximately 60% in all PET positive regions. Therefore, a sample size of 40 participants (i.e., approximately 31 positive regions) is estimated to provide more than 90% power to achieve a lower boundary of a 2-sided 95% exact binomial CI about the estimated region-level PPV that exceeds 30%.

6 RANDOMIZATION AND BLINDING

This is a single arm, non-randomized, open-label study. All participants will receive ^{64}Cu-SAR-BBN and thus blinding of the investigational product is not applicable.

However, to allow for a non-biased assessment of the ^{64}Cu-SAR-BBN PET/CT, the scans will be assessed by three independent central readers, blinded to the participants-specific information (identifiers, medical history, physical exam, laboratory results), the timepoint of the scan, results of evaluations as part of the Reference Standard, results of other imaging modalities, final diagnosis/outcome, and details of the protocol.

To allow for a non-biased assessment of the Reference Standard, an independent central panel of experts will be used to assess and determine the composite Reference Standard. The expert panel will not include any of the three readers who assess the ^{64}Cu-SAR-BBN PET/CT scans. The panel will not have access to the ^{64}Cu-SAR-BBN PET/CT scans or reports from the local or central read of the scans.

7 ANALYSIS SETS

For the purposes of defining the analysis sets, the participants are considered enrolled when they had a Day 0 visit. Unless otherwise specified, data for participants who were enrolled but did not receive a ^{64}Cu-SAR-BBN administration will be listed but will not be included in summary tables. For purposes of analysis, the following analysis sets are defined:

Objective	Description
All Participants Set	All screened participants who signed the informed consent form (ICF). Screen failure information will be summarized using the All Participants Set.
Enrolled Analysis Set	All participants who signed the ICF and were enrolled into the study. This will be used for participant disposition and analysis set summaries.
Safety Analysis Set	All enrolled participants who received any amount of ^{64}Cu-SAR-BBN. This will be used to assess all safety data.

Full Analysis Set (FAS)	All participants who received any amount of ^{64}Cu-SAR-BBN and had ^{64}Cu-SAR-BBN PET/CT imaging results from at least one central reader. This will be used for all efficacy analyses. It should be noted that participants may be include in the FAS but not have sufficient data for inclusion in the analysis of a specific endpoint(s) using the FAS. In this instance the subject will not be included in the analysis of the endpoint despite being included in the FAS and the analysis being conducted using the FAS.
Per Protocol (PP) Analysis Set	All participants in the FAS who had an evaluable assessment of the Reference standard against ^{64}Cu-SAR-BBN PET/CT imaging results for the participant-level and at least one region for the Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT scan, and had no exclusionary protocol deviations that exclude them from PP analysis i.e. participants included in the PP are require to: 1. Have Day 0 and Day 1 central reader results from at least 1 central reader. 2. Have Day 90 SOC imaging and assessed by central reader. 3. Have Day 180 SOC imaging for participants who are deemed to be negative or equivocal for PC recurrence based on central review of the 90-day conventional imaging. 4. Have full dose of ^{64}Cu-SAR-BBN administered. 5. Have not undergone prohibited treatment while on study. 6. For participants that undergo salvage focal therapy, have sufficient PSA data to assess PSA Participants that were replaced on study will not be included. This will be used to repeat the primary and selected secondary efficacy analyses only.
Biodistribution Analysis Set	All participants in the Safety Analysis Set who had at least one biodistribution measure. This will be used to summarize biodistribution data.

8 STATISTICAL METHODS

8.1 General Considerations

8.1.1 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Baseline: A baseline value, unless specified otherwise, is the last non-missing value recorded prior to the ^{64}Cu-SAR-BBN administration. For 12-Lead electrocardiogram, both of the duplicate measurements prior to ^{64}Cu-SAR-BBN administration are defined as Baseline measurement, and the mean of the duplicate measurements is defined as the Baseline value. If an assessment has both date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline. For participants who are enrolled, but not dosed, the last assessment collected on or prior to the enrollment date is considered baseline.
- Change from Baseline: Change from baseline will be calculated for each participant at the specified timepoint as the value at the specified timepoint minus the baseline value.
- Study Day: The day of ^{64}Cu-SAR-BBN administration will be Day 0 as specified in the study protocol schedule of events, but for Clinical Data Interchange Standards Consortium (CDISC) compliance, the study day variables will consider this as "Day 1" as there cannot be a Day 0. For the Study listings and tables the character/text values for the "Visit" variable for Day 0 visit will present as "Day 0" to match the protocol; the numeric values for the "Study Day" variable will be derived as follows:
    - For a given date, study day is calculated in the Study Data Tabulation Model (SDTM) data as days since the date of administration of ^{64}Cu-SAR-BBN:
        - Study day = date – dose date + 1, where date ≥ dose date
        - Study day = date – dose date, where date < dose date
    - For a given date, study day is calculated in the TFL presentations as days since the date of administration of ^{64}Cu-SAR-BBN:
        - Study day = date – dose date, where date ≥ dose date
        - Study day = date – dose date, where date < dose date
- Days: Durations, expressed in days, between one date (date1) and another later date (date2) are calculated as: duration in days = (date2 – date1 + 1).
- Body Mass Index (BMI): BMI (kg/m^2) = weight (kg) / [height (m)]^2.

8.1.2 Summarization Groupings

The summary tables will be presented by visit, timepoint (when applicable), and central reader (for efficacy analyses). As this is a single-arm study, only one group will be reported per analysis set.

8.2 General Comments on the Statistical Analyses

- Age will be computed from the informed consent date and the date of birth.
- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum.
- Categorical data will be reported with frequency counts and percentages.
- All relevant data captured on the electronic case report forms (eCRFs) and from external laboratories including specific descriptions of "other" and comments fields will be provided in by-participant listings. All listings will be sorted by participant identifier and visit in ascending order.
- If a clinical laboratory result is reported relative to a lower/upper range of detection for an assay, for example, "<10", the numeric portion of the result (10) will be used for statistical analyses and the full result, including any symbols, will be provided in the participant listings.
- Analysis Data Model (ADaM) datasets will be prepared using CDISC ADaM Version 2.1 or later, and CDISC ADaM Implementation Guide Version 1.1 or later. Pinnacle 21 Community Validator Version 3.1.2 or later will be utilized to ensure compliance with CDISC standards.
- SAS Version 9.4 (or higher) will be used to provide all TFLs.

8.3 Handling of Missing Data

- Missing values for individual datapoints will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations unless otherwise indicated. For the reference standard, expert panel adjudications will never be missing and will be assigned as "non-evaluable" if based on missing data. Sensitivity analyses will be performed for non-evaluable reference standard assessments.
- Dates will be presented in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are missing because they are not applicable for the participants will be output as "NA", unless otherwise specified. In cases of missing or incomplete dates (e.g., concomitant medications and adverse events), the missing component(s) will be assumed as the most conservative value possible in the derivations of concomitant medication and treatment-emergent adverse event. For example, medications with missing start dates, but with stop dates either overlapping into the study period or missing, will be counted as concomitant,

taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the medication started or ended prior to the ^{64}Cu-SAR-BBN administration. If the above cannot be conclusively established based on the partial and/or present dates, then the medication will be considered as concomitant. Actual data values as they appear in the original eCRFs will be presented in the data listings.

- Where individual datapoints are missing, categorical data will be summarized based on reduced denominators (i.e., only participants with available data will be included in the denominators) unless otherwise indicated.

8.4 Reporting Conventions

In general, the units provided for a result will mirror what is collected on the eCRF unless otherwise specified. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported, mean, median, and quartiles will be displayed to one level of precision greater than the data collected, and the standard deviation/standard error will be displayed to two levels of precision greater than the data collected.

The *p*-values will be reported to 4 decimal places, with values less than 0.0001 reported as "<0.0001" and values greater than 0.9999 reported as ">0.9999".

8.5 Replacement of Participants

Participants who did not complete all required study visits (including those who received prohibited treatment and were discontinued early) may be replaced if needed to achieve the target sample size. Participants who withdrew prior to receiving investigational product will be replaced.

The study team will meet periodically to determine if such participants need to be replaced.

8.6 Calculation of PSA Doubling Time and PSA Velocity

The following values of PSA are collecting for this study:

- PSA at initial diagnosis
- Nadir PSA after initial definitive treatment
- Most recent PSA prior to ^{64}Cu-SAR-BBN dosing #1 and #2
- Screening PSA
- PSA taken during the study at day 90 and 180 (if appliable) or after start of salvage focal therapy (can vary)

PSA doubling time (PSADT) and PSA velocity will be calculated using the Memorial Sloan-Kettering Cancer Center Nomogram at baseline and during the study. PSA at initial diagnosis will not be used for any calculations of PSA velocity or PSADT.

- At least 3 PSA datapoints should be captured to calculate PSA velocity.
- For calculation of PSA velocity at Baseline, all available data within 12 months prior to screening as well as screening value (excluding at initial diagnosis) will be used.
- For calculation of PSA velocity Post-Baseline, all available data on-study, including screening value, will be used. If the participant initiated radiation therapy on-study, the last PSA value is instead the last PSA value PRIOR to initiating radiation therapy.
- For calculation of PSADT at Baseline, PSADT = ln(2) / ((ln(PSA value at screening) – ln(oldest PSA value within 12 months prior to screening)) / (# of months from oldest PSA value within 12 months prior to PSA at screening))
- For calculation of PSADT Post-Baseline, PSADT = ln(2) / ((ln(Last on-study PSA value) – ln(PSA at screening)) / (# of months from last on-study PSA value to PSA at screening)). If the participant initiated radiation therapy on-study, the last PSA value is instead the last PSA value PRIOR to initiating radiation therapy.
- If a participant has no post-screening value prior to initiation of radiation therapy, they will be excluded from post-baseline calculations of PSADT and PSA velocity.

For the calculation of the line of best fit for PSA velocity, the following equations will be used for each participant, where x_i is the date of the measurement in months from screening (screening is $x = 0$) for each value, y_i is the PSA value, and n is the total number of datapoints for the participant for that calculation:

$$\bar{X} = \frac{\sum_{i=1}^{n} x_i}{n}, \quad \bar{Y} = \frac{\sum_{i=1}^{n} y_i}{n}$$

$$PSA\ Velocity = \frac{\sum_{i=1}^{n}(x_i - \bar{X})(y_i - \bar{Y})}{\sum_{i=1}^{n}(x_i - \bar{X})^2}$$

8.7 ^{64}Cu-SAR-BBN PET/CT Imaging Scans and Status Assessment

The ^{64}Cu-SAR-BBN PET/CT scans at Day 0 and Day 1 will be interpreted locally in a non-blinded fashion, and centrally by three different independent blinded readers. Each reader will be required to evaluate the PET/CT scans individually for the presence of pathological ^{64}Cu-SAR-BBN uptake in the regions of prostate bed/gland, pelvic lymph nodes, extra pelvic lymph nodes, visceral/soft tissue and bone. Both local and central interpretations will determine the number of PET-positive lesions in each region and subregion. The regions and subregions that will be assessed on the ^{64}Cu-SAR-BBN PET/CT scans are listed as follows:

	Anatomic Region	**Subregions**

1	Prostatic	1. Prostate Gland or Prostate Bed
2	Pelvic lymph nodes	1. Right Pelvic 2. Left Pelvic 3. Other Pelvic
3	Extra pelvic lymph nodes	1. Retroperitoneal 2. Supradiaphragmatic 3. Other Extra-Pelvic
4	Visceral/soft tissue *Note: This region is incorrectly labeled as Region 5 in the raw data and will be recoded.*	1. Lung / Pleura 2. Liver 3. Other Soft Tissue / Visceral
5	Bone *Note: This region is incorrectly labeled as Region 4 in the raw data and will be recoded.*	1. Pelvic Bone – R 2. Pelvic Bone – L 3. Skull 4. Clavicle – R 5. Clavicle – L 6. Scapula – R 7. Scapula – L 8. Sternum 9. Ribcage – R 10. Ribcage – L 11. Spine 12. Extremities 13. Other bone lesion

The three central reader interpretations will be used in the analysis of efficacy endpoints. Subregion, region, and participant-level ^{64}Cu-SAR-BBN status (i.e. positive, negative, non-evaluable) will be derived.

For the central reader image review the study database will capture subregion assessments for both PET and CT images individually.

The process for the central interpretation of the Day 0 and Day 1 ^{64}Cu-SAR-BBN PET scans was amended during the study. Scans read prior to 22 AUG 2024 had both unequivocal and equivocal lesions (using the definition provided in section 8.3.2 of the protocol) recorded by the readers. The status of each subregion was then derived based on the presence of lesions as equivocal (if only equivocal lesions were present in the subregion), unequivocal (if at least 1 unequivocal lesion was present in the subregion) or negative (if no equivocal or unequivocal lesion was present in the subregion). For the purposes of data analysis and interpretation, any equivocal findings on scans read prior to 22 AUG 2024 will be handled and presented as negative findings.

Scans read after 22 AUG 2024 only had unequivocal lesions recorded by the readers (i.e. equivocal lesions were no longer recorded), and these unequivocal lesions were recorded as positive, cluster, or diffusions. For scans read after 22 AUG 2024 the status of each subregion was then derived based on the presence of lesions as positive (i.e. if at least 1 positive lesion, cluster or diffusion was present in the subregion) or negative (if no positive lesion, cluster or

diffusion was present in the subregion). For the purposes of data analysis and interpretation, for scans read after 22 AUG 2024, findings recoded as positive, cluster, and diffusions, (formerly defined as unequivocal, unequivocal – cluster, and unequivocal diffusions respectively) will be considered as positive and presented as a positive finding.

The derivation of ^{64}Cu-SAR-BBN status on Day 0 or Day 1 will be based on the assessment for the PET images only.

For the purposes of the remainder of this document, ^{64}Cu-SAR-BBN lesions recorded as unequivocal, positive, cluster or diffusion (depending on the date at which they were assessed) will be referred to as "unequivocal".

The status of a subregion (i.e. positive or negative) for the ^{64}Cu-SAR-BBN result on Day 0 or Day 1 is defined as the following:

- A subregion is considered ^{64}Cu-SAR-BBN PET/CT positive if it has at least one unequivocal PET-positive lesion.
- If a subregion is marked as non-evaluable, then the subregion is non-evaluable and cannot be used in the comparison with the reference standard, this will be excluded from the analysis for that participant.
- If the subregion is not marked as non-evaluable but there are no unequivocal lesions present, the subregion is considered negative.

For derivations of ^{64}Cu-SAR-BBN Day 0 or Day 1 positive status:

- A subregion is considered ^{64}Cu-SAR-BBN PET/CT positive if it has at least one unequivocal PET-positive lesion.
- A region is considered ^{64}Cu-SAR-BBN PET/CT positive if it has at least one subregion that is considered positive (at least one unequivocal PET-positive lesion).
- A participant is considered ^{64}Cu-SAR-BBN PET/CT positive if this participant has at least one region that is considered positive.

Handling and presentation of the local reader and central reader ^{64}Cu-SAR-BBN PET/CT data is further described in section 10.13.

Assessment of ^{64}Cu-SAR-BBN PET/CT scan results against the reference standard is described in section 8.9.

8.8 Reference Standard and Status Assessment

A reference datapoint is a follow-up histopathology assessment, PSA response, or imaging scan (with the exception of the ^{64}Cu-SAR-BBN PET/CT scans) occurring between Day 1 and Day 180 that is used to confirm if PC is demonstrated at participant-, region- and subregion-level. All reference datapoints on study will be evaluated by the expert reference panel to determine the reference standard for each participant. The results will be indicated as "positive", "negative", "inconclusive/equivocal", or "non-evaluable". Additional details are provided in the Reference Standard Review Panel Manual.

Note: An "inconclusive" finding (as described in the protocol and imaging manuals) will be assigned to the value of "indeterminate" in the transfer dataset for the central reader histopathology results. As such, for the data analysis and presentation of histopathology findings the terms "inconclusive" and "indeterminate" are considered to have the same meaning and will be used interchangeably. This was implemented in the central reader histopathology database, as for other CDISC SDTM variables that require controlled terminology, "indeterminate" is the defined submission value, with acknowledgement that "inconclusive" is a defined CDISC synonym for this term (to allow for the connection of NCI preferred terms with SDTM submission values).

The handling and presentation of the reference standard data is described in section 10.14, with the handling and presentation of the individual components contributing to the reference standard discussed in section 10.11 (for conventional SOC imaging and histopathology data) and section 10.15.3.6 (for PSA data).

The composite Reference Standard will be assessed against the ^{64}Cu-SAR-BBN results at region-level and participant-level; described further in section 8.9.

8.9 Definitions for Assessments of the Reference Standard against ^{64}Cu-SAR-BBN PET/CT Results

Assessment of the Reference Standard against ^{64}Cu-SAR-BBN PET/CT results (i.e., assignment of True Positive, True Negative, False Positive or Non-evaluable status) will be undertaken for Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT results separately.

Assessments of **Region-Level** Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results:

- True Positive:
    - Histopathology: A region that is ^{64}Cu-SAR-BBN PET-positive (includes at least one unequivocal PET-positive lesion) and Reference Standard positive is considered a TP region.
    - Imaging: A subregion that is ^{64}Cu-SAR-BBN PET-positive (i.e., includes at least one unequivocal PET-positive lesion) and Reference Standard positive (i.e., includes at least one unequivocal lesion detected on conventional

imaging in that subregion) is considered a TP subregion. The subregion must match between the two assessments. If any region has at least one TP subregion, the region-level status is considered TP.

- True Negative:
    - A region that is ^{64}Cu-SAR-BBN PET-negative (considered evaluable [i.e. not marked as non-evaluable] and no unequivocal PET-positive lesion detected within the subregions) and Reference Standard negative.
- False Positive:
    - A region that is ^{64}Cu-SAR-BBN PET-positive (i.e., includes at least one unequivocal PET-positive lesion) and Reference Standard negative (determined from at least one evaluable timepoint).
- Non-evaluable:
    - A region that has either non-evaluable ^{64}Cu-SAR-BBN PET/CT results for a specific timepoint (Day 0 or Day 1) or has a non-evaluable or inconclusive/indeterminate Reference Standard.

Assessments of **Participant-Level** Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results:

- True Positive:
    - A participant with at least one TP region
    - At least one unequivocal ^{64}Cu-SAR-BBN positive lesion in any region and a confirmed PSA response to radiation or other salvage focal therapy.
        - Confirmed PSA response following radiation or other salvage focal therapy (as long as no concomitant androgen-deprivation therapy (ADT) is given): total PSA decline ≥50% from baseline, confirmed by a second value within four weeks per Prostate Cancer Working Group 3 criteria.
- True Negative:
    - A participant with a negative ^{64}Cu-SAR-BBN PET/CT (i.e., considered evaluable [i.e. not marked as non-evaluable] and no unequivocal PET-positive lesion(s) detected) and negative Reference Standard.
- False Positive:
    - A participant who does not meet the TP criteria and has at least one unequivocal ^{64}Cu-SAR-BBN PET-positive lesion and has an evaluable Reference Standard.

- Non-evaluable:
    - A participant that has either non-evaluable ^{64}Cu-SAR-BBN PET/CT results for a specific timepoint (Day 0 or Day 1) or has a non-evaluable or inconclusive Reference Standard.

False negative results (region- or participant-level) will not be assigned as there is no way to determine whether the disease was initially present, or whether the disease has developed since the acquisition of the baseline and ^{64}Cu-SAR-BBN imaging. For summarization purposes only, these will be considered "Test Negative" that is defined as a negative ^{64}Cu-SAR-BBN PET/CT result within region-level or participant-level and a positive Reference Standard within region-level or participant-level accordingly.

Full programmatic details of the algorithm to derive the subregion-level, region-level, and participant-level results of the assessment of the Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results is outlined in the document labelled:
CLB03_Primary_Analysis_Supplement.xlsx.

8.10 Analysis Visit Windows for Reference Datapoints

A reference datapoint defined in the previous sections can occur at anytime post-Day 1 and Day 180 on study. There are two reference timepoints of interest in the analysis, Day 90 and Day 180. These timepoints (visit labels) are the occasions at which information was collected on clinical events that occurred between the previous visit/reference timepoint and the current visit/reference timepoint, i.e., the visit/reference timepoint represents events that occurred over a window of time up to that visit/reference timepoint and does not represent only events which occurred at the specific timepoint/day. The following describes the analysis windows surrounding these analysis visits:

- The visit described in the visit form completed for the assessment will be used as the analysis visit.
- If the visit is considered unscheduled or out of the protocol defined visit windows (Day 75-105 for Day 90 and 165-195 for Day 180), then the following analysis visit windows are used:
    - Day 90 Analysis Visit: Day 2 – Day 120 (or first analysis visit post-baseline)
    - Day 180 Analysis Visit (only if a Day 90 already exists): Day 121 – End of Study.

9 DEVIATIONS FROM PROTOCOL ANALYSIS

In the event of minor changes or inconsistencies between the planned statistical analyses in the SAP and the protocol, the SAP should take precedence. The deviation(s) from protocol analysis is listed as follows:

For the exploratory analyses investigating the efficacy endpoints as a function of baseline variables, biodistribution lesion-to-background ratio was included as one of the baseline variables to be used. However, lesion-to-background ratios in not deemed as informative or necessary and has been removed from the list of baseline variables to investigate.

10 STATISTICAL ANALYSIS

10.1 Screened Participants

Using the All Participants Set, the number of screened participants as well as the number and percentage of participants who were enrolled and reasons for non-enrollment will be summarized. Inclusion/exclusion findings will also be listed.

10.2 Participant Disposition

Participant disposition will be summarized for the Enrolled Analysis Set. Summaries will include:

- Number of participants who completed the study
- Number of participants who discontinued from the study and reason for discontinuation.

Participant disposition data will also be presented in listings.

10.3 Analysis Sets

Using the Enrolled Analysis Set, the number and percent of participants in the Safety, FAS, PP, and Biodistribution Analysis Sets will be provided. Reasons for exclusion from the FAS, PP and Biodistribution Analysis Sets will be summarized and presented in listings.

10.4 Protocol Deviations

In accordance with International Council for Harmonisation (ICH) E3, Sponsor-defined eligibility violations and major protocol deviations will be identified and listed. Deviations that exclude a participant from the PP Population will also be identified. Protocol deviations will also be tabulated by type of deviation and major deviations will be summarized separately by type of deviation in the Enrolled Analysis Set.

10.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized descriptively for the Safety Analysis Set, FAS, and PP Analysis Set. The following demographic and baseline data will be summarized: age, sex, race, ethnicity, height, weight, BMI, and Eastern Cooperative Oncology Group (ECOG) status. Age is calculated in the Electronic Data Capture (EDC) from date of birth to date of informed consent. A demographic listing will be provided.

10.6 Prostate Cancer Symptoms

The PC symptoms will be summarized by body system, symptom, regardless of whether symptoms are ongoing or have resolved, and by body system, symptom and severity grade (if symptom ongoing) for the Safety Analysis Set. All PC symptom data will be listed.

10.7 Medical and Surgical History

Medical and Surgical history collected at screening will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 25. Medical and Surgical history will be summarized for the Safety Analysis Set by system organ class and preferred term.
Medical and Surgical history will be listed.

10.8 Prostate Cancer Related History

Relevant medical history related to PC will be summarized for the Safety Analysis Set, including initial PC diagnosis (PC pathology results), initial diagnosis stage per American Joint Committee on Cancer (AJCC) classification, initial Gleason score, initial tumor (T) stage, initial node (N) stage, initial metastasis (M) stage, time from initial diagnosis to Day 0, time from biochemical recurrence to Day 0, and PSA levels at biochemical recurrence.

All relevant PC-related history will be listed.

10.9 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) drug dictionary, WHO Drug – Global B3, March 2022.

Prior medications are those medications started before the administration of ^{64}Cu-SAR-BBN. Concomitant medications are those medications taken after the administration of ^{64}Cu-SAR-BBN. As such, prior medications continued after the administration of ^{64}Cu-SAR-BBN are also considered concomitant medications. Prior and concomitant medications will be summarized for the Safety Analysis Set by ATC class (level 4) and preferred term. Participants receiving the same medication more than once are counted only once for each ATC class and preferred name.

The missing component(s) of all medications with partial or missing dates and/or times recorded on the concomitant medication eCRF will be assumed as the most conservative value possible as specified in the Section 8.3.

Prior and concomitant medications will be listed by participant.

10.10 Cancer Therapy, Surgery, and Radiotherapy

PC-related treatments that occurred before and on study will be summarized for the Safety Analysis Set by period and treatment type. The number of historical and on-study cancer therapies, surgeries, and radiotherapies will be summarized by period.

Any cancer therapies, surgeries, and radiotherapies, including start and stop dates, treatment type, treatment regime, and response information will also be listed for each participant.

10.11 Conventional Imaging and Histopathology

Standard of care (SOC) conventional imaging will be performed during screening as part of eligibility into the trial and at Day 90 and 180 (if applicable) to establish the Reference Standard. Furthermore, additional SOC conventional imaging can be completed at investigator discretion within 180 days (±15 days) of Day 0. The imaging type and modality for imaging in each type will be summarized by visit for the FAS. Both local and central reads of these scans at participant-, region-, and subregion-level will be summarized by visit for the FAS and listed for the enrolled analysis set.

Similarly, local histopathology findings will be summarized for the FAS and listed for the enrolled analysis set, including scan type where the lesion was identified, type of histopathology procedure, number of lesions biopsied, and histopathology results at participant-, region-, and subregion-level.

10.12 Study Drug Administration

Participants will receive a single dose of ^{64}Cu-SAR-BBN on Day 0. All ^{64}Cu-SAR-BBN dose pre-administration information, ^{64}Cu-SAR-BBN administration information and ^{64}Cu-SAR-BBN post-administration information collected in the eCRF will be listed. The following information will be summarized for the Safety Analysis Set:

- Number of participants with a complete dose administered and reasons for dose not completely administered
- Activity in syringe before and after injection (MBq)
    - 1 mCi = 37 MBq
- Actual activity of ^{64}Cu-SAR-BBN administered (MBq)
- Method of administration
- Site of administration.

All ^{64}Cu-SAR-BBN administration information will be listed by participant.

10.13 ^{64}Cu-SAR-BBN PET/CT Imaging

^{64}Cu-SAR-BBN PET/CT imaging will be performed on Day 0 and Day 1. The scans will be assessed by a local reader and by the three central readers.

For both local and central readers, all ^{64}Cu-SAR-BBN PET/CT imaging results including evidence of ^{64}Cu-SAR-BBN uptake and number of lesions, will be summarized at the participant-, region-, and subregion-level by timepoint (Day 0 and Day 1).

All ^{64}Cu-SAR-BBN PET/CT results will be listed by participant.

10.14 Reference Standard

The reference standard results, as defined in Section 8.7, including the level of evidence used (Level 1: Histopathology, Level 2: SOC imaging, Level 3: Confirmed PSA response), for the participant-, region-, and subregion-level will be summarized.

All reference standard results for each participant will be listed with information of imaging and histopathology at the participant-, region-, and subregion-level, and confirmation of PSA results at the participant-level where applicable.

10.15 Efficacy Analyses

All efficacy endpoints will be assessed using the FAS with supportive analyses performed with the PP analysis set for the primary efficacy endpoints and selected secondary endpoints. For definitions of ^{64}Cu-SAR-BBN PET/CT positive status criteria see Section 8.7 and for definitions of assessment of ^{64}Cu-SAR-BBN results against the Reference Standard results, see Section 8.8. Alpha level is set to 0.05 for all *p*-values without considering multiplicity, and *p*-values are considered exploratory.

All analyses that are considered "region-level" will be conducted in two ways (unless otherwise specified): the analysis will be conducted on all five regions as a whole (labeled as "All Regions") and by region individually, for six in total.

10.15.1 Primary Efficacy Analyses

The co-primary efficacy endpoints are the following:

- Participant-level CDR at Day 0
- Participant-level CDR at Day 1
- Region-level PPV at Day 0
- Region-level PPV at Day 1.

CDR on a participant-level for each central reader is defined as the proportion of TP participants out of all scanned participants who had at least one evaluable reference standard datapoint collected and is calculated as: CDR (%) = TP/(all scanned participants with at least one evaluable reference datapoint) × 100.

Participants without a ^{64}Cu-SAR-BBN PET/CT scan at the specific timepoint (Day 0 or Day 1) will be excluded from the participant-level CDR calculation for that timepoint. Participants with non-evaluable participant-level Reference Standard results will be excluded from the CDR calculation.

PPV is measured on a region-level for each central reader and is defined as the proportion of TP regions out of all positive regions on the ^{64}Cu-SAR-BBN PET/CT scan with corresponding evaluable composite Reference Standard data and will be calculated as: PPV (%) = TP/(TP + FP) × 100, where FP = False Positive.

Regions that are not positive on the ^{64}Cu-SAR-BBN PET/CT scan at a specific timepoint will be excluded from the region-level PPV for that timepoint. PET/CT positive regions without corresponding evaluable composite Reference Standard results will also be excluded.

The anatomic regions for the PPV calculation are the following:

- Region 1 = Prostatic
- Region 2 = Pelvic lymph nodes
- Region 3 = Extra pelvic lymph nodes
- Region 4 = Visceral/soft tissue (*Note: This region is incorrectly labeled as Region 5 in the raw data and will be recoded.)*
- Region 5 = Bone (*Note: This region is incorrectly labeled as Region 4 in the raw data and will be recoded)*.

CDR and PPV will be summarized by central reader at Day 0 and Day 1 for participants who had at least one reference datapoint, along with the 2-sided 95% binomial CIs using the Clopper-Pearson Exact method. All primary endpoints will be summarized for the FAS (participants within the FAS without sufficient results to construct the required outcome variable for the endpoint, e.g., a participant without an evaluable reference datapoint cannot contribute to the determination of CDR, will by nature not be included in the respective endpoint analysis) and will be repeated in PP Analysis Set as supportive analyses.

Histogram panels will be presented to display the participant-level CDR and region-level PPV by central reader at Day 0 and Day 1 in the FAS analysis set.

10.15.1.1 Sensitivity Analysis for the Primary Endpoints

The following sensitivity analysis will be conducted on all participants in the FAS regardless of whether there are reference datapoints collected. Missing data will be handled in two different ways:

- Worst-case Imputation:
    - For the participant-level CDR on Day 0 and 1, participants with missing, non-evaluable, or inconclusive Reference Standard data will be imputed as non-TP and will be included in the denominator. The results will be presented in the same way as the primary analysis for CDR.
    - For the region-level PPV on Day 0 and 1, PET/CT positive regions with missing, non-evaluable, or inconclusive Reference Standard data will be

imputed as FP. The results will be presented in the same way as the primary analysis for PPV.

- Tipping Point Analysis:
    - A tipping point analysis will be performed for both participant-level CDR and region-level PPV, where participants with missing or non-evaluable Reference Standard data will be imputed as TP with probability p ranging from 0 to 1 with an increment of 0.1, and PET/CT detected regions with missing, non-evaluable, or inconclusive Reference Standard data will be imputed as TP with probability p.
    - For participant-level CDR, p = 0 denotes none of the participants in the Reference Standard with missing data will be imputed as TP while p = 1 denotes all participants in the Reference Standard with missing data will be imputed as TP. For region-level PPV, the meaning of p is similarly addressed for PET/CT detected regions.
    - For each of the 11 values of p (0 - 1 by 0.1), 20 imputation datasets will be constructed and combined, where the value of p is the probability that the imputation will be TP. The results will be presented in the same way as the primary analysis for CDR and PPV for Day 0 and 1 without the 95% CIs.
    - Figures displaying the CDR or PPV curve of point estimates for each value of p will be presented.

10.15.2 Secondary Efficacy Analyses

The following secondary analyses will be performed in a similar manner as the primary analysis, and will be summarized by central reader with point estimates and exact Clopper-Pearson 95% CIs in the FAS and repeated with the PP Analysis Set:

- Participant-level PPV at Day 0 and Day 1
    - PPV (%) = TP/(TP + FP) × 100.
- Participant-level DR at Day 0 and Day 1
    - DR (%) = (number of participants with positive ^{64}Cu-SAR-BBN PET/CT scan)/(all participants with a ^{64}Cu-SAR-BBN PET/CT scan) × 100.
- Participant-level FPR on Day 0 and Day 1
    - FPR (%) = FP/(all participants with a positive ^{64}Cu-SAR-BBN PET/CT scan and an evaluable reference standard) × 100.
- Region-level FPR at Day 0 and Day 1
    - FPR (%) = FP regions/(all positive regions on the ^{64}Cu-SAR-BBN PET/CT scan and an evaluable reference standard) × 100.

- Participant-level discrepant PET negative rate between Day 0 and Day 1 for reference standard positive participants
    - Discrepant PET negative rate (%) = (number of participants with participant-level discrepancy in ^{64}Cu-SAR-BBN results between Day 0 and 1)/(all participants with a positive reference standard) × 100.
- Participant-level True Negative Rate (TNR) on Day 0 and Day 1
    - TNR (%) = TN/(TN+FP) × 100.
- Region-level TNR at Day 0 and Day 1
    - TNR (%) = TN/(TN+FP) × 100.
- Region-level Apparent Negative Predictive Value (ANPV; referred to as TNR in protocol) at Day 0 and Day 1;
    - TN/(number of regions with a negative ^{64}Cu-SAR-BBN result).

Discrepant Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT results (results differ within subregion from Day 0 and Day 1 within the same central reader) will also be listed.

10.15.3 Exploratory Efficacy Analyses

The following exploratory analyses will be performed on the FAS for each central reader.

10.15.3.1 Composite ^{64}Cu-SAR-BBN PET/CT Day 0 and Day 1 Results

CDR, participant- and region-level PPV, and DR, as described in the primary and secondary analyses, will be analyzed separately with the proportions derived using the best outcome from both Day 0 and Day 1.

For the composite CDR and PPV a participant or region (if applicable) will be classed as TP if they meet one of the following criteria:

- Classed as TP on Day 0 (regardless of classification on Day 1)
- Classed as TP on Day 1 (regardless of classification on Day 0).

For the composite PPV a participant or region will be classed as FP for the denominator if they meet one of the following criteria and are not classed at TP based on the composite PPV TP criteria above:

- Classed as FP on Day 0 and Day 1
- Classed as FP on Day 0 and classed as either TN, test-negative or non-evaluable on Day 1
- Classed as FP on Day 1 and classed as either TN, test-negative or non-evaluable Day 0.

For DR a participant will be classed as having a positive composite ^{64}Cu-SAR-BBN PET/CT scan if they meet one of the following criteria:

- A positive ^{64}Cu-SAR-BBN result on both Day 0 and Day 1
- A positive ^{64}Cu-SAR-BBN result on Day 0 and negative, or missing^{64}Cu-SAR-BBN result on Day 1
- A negative, or missing ^{64}Cu-SAR-BBN result on Day 0 and a positive ^{64}Cu-SAR-BBN result on Day 1.

The total number of scanned participants (i.e., the denominator for DR) will be the number of participants who underwent a ^{64}Cu-SAR-BBN PET/CT scan on both Day 0 and Day 1.

The composite CDR, participant- and region-level PPV, and DR will be summarized with the 95% exact Clopper-Pearson CIs for each central reader.

10.15.3.2 Function of Baseline and Other Variables of Interest

CDR, participant- and region-level PPV, and DR of both the Day 0 and Day 1 scans will be summarized by the following variables:

- PSA at baseline: <0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5.0 ng/mL
- PSA doubling time at baseline (PSADT): 0-<3.0, 3.0-8.9, 9.0-14.9, ≥15.0 months
    - Participants with a negative PSADT at baseline will be included in the ≥15.0 months group.
- PSA velocity at baseline: <0.05, 0.05 - <0.10, 0.10 - <0.20, ≥0.20 ng/mL/y
- Testosterone at baseline: <230, 230 - 350, ≥350 ng/dL
- Standardized uptake value (SUV) max: SUVmax category cut-off values will be determined from the data with data separated into quartiles, allowing for an approximately equal distribution of subjects within each of the 4 SUVmax groups.
- Prior treatment received (2 categories): radical prostatectomy OR definitive radiation therapy.
- Reference Standard Level of Evidence Used: Level 1, Level 2, Level 3
    - Level 1: Histopathology (regardless of imaging results or PSA response being available),
    - Level 2: SOC imaging (regardless of PSA response being available) but no contributing histopathology information,
    - Level 3: Confirmed PSA response ((i.e., no contribution of histopathology or imaging result information (participant-level only)).
- Size of largest lesion (longest diameter) identified on ^{64}Cu-SAR-BBN PET/CT central reader scan: 0 - <0.5, 0.5 - <1.0, ≥1.0 cm
- Time to ^{64}Cu-SAR-BBN PET/CT scan from dosing (Day 0 only): 1 - 2 hours, 2 - 4 hours.

CDR, participant and region-level PPV, and DR will be summarized for each level of the categorical variables by central reader. Region-level parameters will only be summarized for the "All regions" category and not the individual regions.

10.15.3.3 PET-positivity versus True/False Positivity

Biodistribution variables, such as mean and max SUV, lesion-to-background ratio, and lesion size in all lesions, visceral/soft tissue lesions, and bone lesions, will be compared individually between participant-level TP and FP groups at Day 0 and Day 1 by central reader in the Biodistribution Analysis Set using a Wilcoxon rank sum test at region-level. Median values of the biodistribution variables at region-level will be summarized for the TP and FP groups by central reader.

Biodistribution variables will be presented with boxplots for the TP and FP groups.

10.15.3.4 Number of Lesions and Number of Positive Regions on Day 0 vs. Day 1

The total number of lesions and positive regions detected per participant on the Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT scans, and the difference of the number of lesions and positive regions detected per participant on the Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT scans will be summarized descriptively by central reader. Comparisons of Day 0 vs. Day 1 will be performed using a Wilcoxon signed rank test by central reader.

10.15.3.5 Lesion-level Overall Agreement

The following scans will be assessed for overall lesion-level agreement rate:

- Day 0 vs. Day 1 ^{64}Cu-SAR-BBN PET/CT scans
- Day 0 ^{64}Cu-SAR-BBN PET/CT scan vs. SOC Scan for the Day 90 Analysis Visit
- Day 0 ^{64}Cu-SAR-BBN PET/CT scan vs. SOC Scan for the Day 180 Analysis Visit
- Day 1 ^{64}Cu-SAR-BBN PET/CT scan vs. SOC Scan for the Day 90 Analysis Visit
- Day 1 ^{64}Cu-SAR-BBN PET/CT scan vs. SOC Scan for the Day 180 Analysis Visit

  Overall agreement rate (%) is defined as the (total number of lesions with matching subregions counted from both scans being analyzed across all patients) / (total number of lesions identified across both scans being analyzed by either imaging across all patients) × 100. All subregions will be used for the agreement rate across all anatomical regions. The overall agreement rate for the comparisons above will be presented by central reader.

  If multiple scans of the same type (e.g., bone scans) occur within an analysis window, then the later (i.e. most recent) scan's outcome will be used in the analysis for a given subregion. For example, if 2 bone scans occur within the Day 90 Analysis Visit where the first Scan has Subregion X with no unequivocal lesions and second Scan (i.e. most recent scan) has Subregion X with 1 unequivocal lesion, then the value for the Day 90 Analysis Visit is that

Subregion X has 1 unequivocal lesion (if the subregion in question is evaluable based on the later scan).

10.15.3.6 PSA Measures Change from Baseline

Total PSA, PSA velocity, and PSADT values will be summarized descriptively at each timepoint including a change from baseline. Boxplots showing the mean, median, Q1, Q3, and outliers for each PSA measure will be presented for each timepoint to investigate PSA over time.

Additional summaries of total PSA, PSA velocity, and PSADT values will be presented for the following subgroups:

- Participants who received salvage focal therapy
- Participants who were TP for the primary analysis at the participant-level
- Participants who were FP for the primary analysis at the participant-level
- Participants who were TN for the primary analysis at the participant-level.

All PSA, PSA velocity (including local lab reported PSA velocity and model derived PSA velocity), and PSADT values will be listed.

10.15.4 Intra and Inter-reader Variability

10.15.4.1 Intra-reader Variability

Sample size calculations were performed to determine the number of Day 0 and Day 1 scans to be re-read by the central readers to assess for intra-reader variability. The proportion of positive/negative ^{64}Cu-SAR-BBN PET/CT scans for PC was assumed to be the same as for results seen in a similar study of ^{18}F-DCFPyL-PCT/CT (the CONDOR study: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8382991/), where 62% were positive, 38% negative, with a Kappa of 0.917 for the intra-reader variability. Using a Kappa for the null hypothesis of 0.3, a sample size of 16 re-reads provides 91% power with one-sided type I error of 0.025 for the intra-reader variability analysis for each timepoint (16 re-reads at Day 0 and 16 at Day 1).

A random subset of 16 participants' Day 0 or Day 1 ^{64}Cu-SAR-BBN PET/CT scans will be evaluated twice by each of the central readers in order to assess the reproducibility of the readings and consistency among the readers. A total of 16 Day 0 and 16 Day 1 scans will be re-evaluated (they may not be the same participants as each timepoint will be randomized separately). The results from the second evaluation will only be used for intra-reader variability assessment and in no other analyses.

For each scan evaluated twice, both the original and 2nd evaluation results will be summarized for each region- and participant-level for ^{64}Cu-SAR-BBN PET/CT positivity and total number of positive lesions. The intra-reader variability will be assessed for each reader separately using

Cohen's pairwise Kappa statistics along with 95% CIs for the dichotomous results (PET-positive or not), and the percent agreement (Lin's concordance correlation coefficient (CCC)), along with 95% CI, for the continuous result (average number of positive lesions) for all participants that have two scan interpretations on a participant-level and region-level. The interpretation of Lin's concordance correlation coefficient according to McBride et al. is presented in Table 1, and the interpretations of Cohen's kappa are presented in Table 2.

Table 1 Lin's concordance correlation coefficient (CCC)

Value of the Lin's CCC	Interpretation
>.99	Almost Perfect
.95–.99	Substantial
.90–.95	Moderate
<0.90	Poor

Table 2 Cohen's Kappa Levels of Agreement

Value of Kappa Level of Agreement % of Data that are Reliable

0–.20	None	0–4%
.21–.39	Minimal	4–15%
.40–.59	Weak	15–35%
.60–.79	Moderate	35–63%
.80–.90	Strong	64–81%
Above .90	Almost Perfect	82–100%

The second evaluation of the scans by the central readers will include all of the same datapoints as the first, original evaluation. The following variables will be assessed for intra-reader variability:

- Participant and region-level ^{64}Cu-SAR-BBN PET/CT positivity described in the primary endpoint analysis.
- Average number of positive lesions at participant and region-level.

10.15.4.2 Inter-reader Variability

For dichotomous results of ^{64}Cu-SAR-BBN PET/CT positivity, the agreement among the 3 independent readers will be assessed in pairs by calculating the percent pairwise concordance, defined as: (# of concordant values across the 2 readers) / (# of concordant values + # of discordant values across the 2 readers) with evaluable ^{64}Cu-SAR-BBN PET/CT data. Additionally, Fleiss's overall multi-assessor Kappa statistics with 95% CIs will be presented for all 3 readers together for the same parameter. Day 0 and Day 1 ^{64}Cu-SAR-BBN PET/CT scans will be analyzed individually.

For the continuous measures related to the total number of positive lesions for participant-level and the 5 regions individually, intraclass correlation coefficient (ICC) will be presented with

95% CIs. Additionally, Bland-Altman plots will be produced to assess the agreement visually for the 6 points. This will be done as reader 1 vs. reader 2, reader 1 vs. reader 3, and reader 2 vs. reader 3.

The following variables will be assessed for inter-reader variability:

- Participant and region-level ^{64}Cu-SAR-BBN PET/CT positivity.
- Number of positive lesions at participant and region-level.

10.15.5 Disease Management

The impact of the ^{64}Cu-SAR-BBN PET/CT Day 0 or Day 1 scan local evaluation will be assessed by the change of intended PC treatment via the Disease Management Form completed at screening (Pre-^{64}Cu -SAR-BBN) and at Day 7 (Post-^{64}Cu -SAR-BBN). These forms will be completed by the treating physician to document whether any change in planned disease management was warranted due to the local ^{64}Cu-SAR-BBN PET/CT findings.

The proportion of participants with any change in intended PC treatment due to Day 0 scan only, Day 1 scan only, both Day 0 and Day 1 scans, and Day 0 or Day 1 scan, will be summarized along with the binomial exact Clopper-Pearson 95% CI.

All disease management data for both timepoints will be listed.

10.16 Safety Analyses

All safety analyses will be conducted on the Safety Analysis Set. Where applicable, participants will be summarized by visit and timepoint.

10.16.1 Adverse Events

Pre-treatment AEs are defined as AEs that have an onset on or after the date the informed consent was signed but before the time of the administration of ^{64}Cu-SAR-BBN. Treatment-emergent adverse events (TEAEs) are defined as AEs that start or worsen after the administration of ^{64}Cu-SAR-BBN.

All AEs with partial or missing dates and times will be considered treatment-emergent unless a partial start date and/or time indicates the AE began before the administration of ^{64}Cu-SAR-BBN or a stop date indicates the AE ended before the administration of ^{64}Cu-SAR-BBN.

All AEs will be coded to system organ class and preferred term according to MedDRA, version 25. The severity (intensity) for each AE reported during the study will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria:

- Mild (Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Moderate (Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)
- Severe (Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Life-threatening (Grade 4): Life-threatening consequences; urgent intervention indicated
- Fatal (Grade 5): Death related to AE.

The causal relationship of the AE to the investigational product will be assessed by the Investigator (or medically qualified delegate) using the following classifications:

- Related
- Not related.

An AE or adverse reaction is considered serious (SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Requires hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Summaries will be provided for TEAEs, with the number and percentage of participants reporting each type of event presented. If a participant has AEs of the same preferred term more than once, it is counted only once within that category. Similarly, if a participant has AEs of two or more preferred terms under the same system organ class, then that participant only counts once for that system organ class.

The following summaries for AEs will be provided:

- An overall summary table of AEs summarizing the number and percent of participants, in the following categories: any AEs, any TEAEs, TEAEs related to study drug, any serious TEAEs, TEAEs leading to study drug withdrawal, TEAEs leading to discontinuation from the study, TEAEs leading to death, and TEAEs by maximum severity grade
- Incidence of TEAEs by MedDRA system organ class and preferred term
- Incidence of TEAEs by MedDRA system organ class, preferred term, and maximum severity grade

- Incidence of study drug-related TEAEs by MedDRA system organ class, preferred terms, and maximum severity grade
- Incidence of TEAEs grade 3 or higher by MedDRA system organ class and preferred term
- Incidence of study drug-related TEAEs grade 3 or higher by MedDRA system organ class and preferred term
- Incidence of SAEs by MedDRA system organ class and preferred term
- Incidence of study drug-related SAEs by MedDRA system organ class and preferred term.

All AE data will be listed by participant.

10.16.2 Clinical Laboratory Evaluations

Safety laboratory parameters (hematology, biochemistry, coagulation, eGFR, urinalysis, and serum testosterone) and the corresponding changes from baseline will be descriptively presented by visit. The incidence of abnormalities will be summarized by measurement timepoint with counts and percentages of participants for the selected laboratory parameters if applicable (L, < Lower Limit of Normal (LLN) or H, > Upper Limit of Normal (ULN)). Shift tables based on the NCI-CTCAE v5.0 toxicity grading (Grade 0: absence of the condition, Grade 1, Grade 2, Grade 3, Grade 4) will be presented for the selected laboratory parameters between baseline and the worst post-baseline grades.

All clinical laboratory data will be listed by participant, and any clinically significant abnormalities in laboratory values will be flagged, i.e., values outside the laboratory reference range will be flagged as low (L, < LLN) or high (H, > ULN), if reference ranges are available.

10.16.3 Vital Signs

The selected vital parameters, weight (kg), BMI (kg/m^2), systolic and diastolic blood pressures (mmHg), will be summarized using descriptive statistics at all scheduled timepoints. Descriptive statistics of the change from baseline to each post-baseline timepoint will also be provided. All vital sign data (systolic and diastolic blood pressures (mmHg), heart rate (bpm), respiratory rate (breaths/minute), body temperature (C), height (cm), weight (kg), and BMI (kg/m^2)) will be listed by participant.

10.16.4 Electrocardiogram (ECG) Parameters

Duplicate 12-lead ECGs will be captured pre-dose and post-dose on Day 0 along with abnormal findings and clinical interpretations. The mean of the duplicate ECG values will be calculated that is used for change from baseline calculations.

The values of the ECG parameters: heart rate, RR interval, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval, as well as the changes from baseline will be summarized using descriptive statistics at all scheduled timepoints. The incidence of

abnormalities will be summarized by measurement timepoint with counts and percentages of participants for the ECG overall interpretation (normal, abnormal but not clinically significant, abnormal and clinically significant). Shift tables will be provided for changes from baseline to worst post-baseline assessment using the categories of normal, abnormal but not clinically significant, and abnormal and clinically significant. For duplicate readings at a single timepoint, the result with the greater clinical significance will be used for the shift table category assignment.

Furthermore, the number and percentage of participants with QTcF and QTcB values that fall into the following categories post-dose will be summarized:

- ≤ 450 msec
- > 450 and ≤ 480 msec
- > 480 and ≤ 500 msec
- > 500 msec.

In addition, the number and percentage of participants with the following post-dose increases in QTcF and QTcB will be summarized:

- ≤ 30 msec
- > 30 - 60 msec
- > 60 msec.

A listing of ECG data will also be provided and will include the overall tracing assessment of normal, abnormal and clinically significant status for these measurements.

10.16.5 Physical Examination

Physical examination findings will be listed by body system. Abnormal findings will be described.

10.17 Biodistribution Analysis

For the Biodistribution Analysis Set, the biodistribution measures for ^{64}Cu-SAR-BBN, such as mean and max SUV, lesion longest diameter, lesion longest perpendicular diameter, lesion-to-background ratio, and reader confidence levels will be summarized descriptively for unequivocal lesions only. Mean and max SUV will use the mean of all unequivocal lesions within a participant to summarize SUV in all unequivocal lesions. Separately the mean and max SUV will be summarized in unequivocal lesions in visceral/soft tissues and lesions in bone. Boxplots will be provided for the biodistribution measures.

Additional summaries of the biodistribution measures described above will be provided for the following subgroups:

- Participants who were TP for the primary analysis at the participant-level
- Participants who were FP for the primary analysis at the participant-level.

All biodistribution measurements along with reader confidence levels will be listed for each participant.

All individual, mean and max SUV, and SUVr measurements in organ, all lesions, visceral/soft tissue lesions, and bone lesions will be listed for each participant without being combined or averaged and will also include the value averaged over all lesions within participant that is used in the summaries.

11 PROGRAMMING SPECIFICATIONS

All available data will be presented in participant data listings, which will be sorted by participant identifier and where appropriate, measurement timepoint and measurement date and time.

The programming specifications, including the mock-up analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents.

APPENDIX A: SCHEDULE OF ASSESSMENTS

	Screening[1]	^{64}Cu-SAR-BBN PET/CT			Safety Visit	Follow-Up	
Study Days	28 days	Day 0		Day 1	Day 7 (±2 days)	Day 90 (±15 days)	Day 180 (±15 days)
Visit	1	2		3	4	5	6[2]
Timeline		Pre Dose	Post Dose	24h (±6h) Post Dose			
Informed Consent[3]	X						
Inclusion/Exclusion	X						
Demographics and Disease Characteristics[4]	X						
Medical and Medication History[5]	X						
Prior Cancer Treatments	X						
Prostate Cancer Treatments					X	X	X
Physical Exam[6]		X			X		
Body Weight	X	X			X		
Height	X						
ECOG Status[7]	X						
Vital Signs[8]		X	X[9]		X		
Duplicate 12-Lead ECG		X	X[10]				
Hematology[11]	X				X		
Biochemistry[12]	X				X		
Coagulation[13]	X				X		
eGFR (CKD-EPI) in mL/min	X				X		
Serum Testosterone	X						
Urinalysis[14]		X			X		
Total PSA[15]	X					X	X
AEs	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X		
^{64}Cu-SAR-BBN Dose		X					
^{64}Cu-SAR-BBN PET/CT			X[16]	X[17]			
PSMA PET and CT and/or MRI[18]	X						
Review of any other available imaging modalities[19]	X						
Follow-up Conventional Imaging[20]						X	X
Additional Imaging/Histopathology[21]						X	
Disease Management Form	X[22]				X[23]		

Abbreviations: AE = adverse event; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; MRI= magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen.

1. Results of SOC tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 0 may be used; such tests do not need to be repeated for Screening. The required conventional scan(s) must be performed within 60 days of Day 0. Conventional scan(s) performed more than 60 days prior to Day 0 may be repeated as a study screening procedure and reviewed by the Investigator prior to Day 0.
2. Visit 6 is only applicable to participants who were deemed negative or equivocal for PC recurrence based on the Visit 5 follow-up conventional imaging (as per the central expert panel's interpretation).
3. Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before the ^{64}Cu-SAR-BBN administration.
4. Demographic data include: year of birth, race, ethnicity. Baseline disease characteristics include: initial diagnosis stage (per American Joint Committee on Cancer), initial Gleason score, initial diagnosis stage (T, N and M staging), pathology results, date of biochemical recurrence, relevant symptom history including, gastrointestinal, genitourinary and musculoskeletal.
5. Medical history will include evaluation of: relevant past or present diseases or disorders, and relevant surgical history. Medication history within 14 days before signing informed consent should be collected.
6. Physical examination includes assessment of: general appearance, cardiovascular system, respiratory system, and nervous system if vertebral involvement.
7. ECOG Scale is used by the Investigator to determine the score (0 to 5) that best represents the participants' activity status.
8. Vital signs include: body temperature, respiratory rate, heart rate and systolic and diastolic blood pressure.
9. Post-dose vital signs to be completed prior to the ^{64}Cu-SAR-BBN PET/CT.
10. Post-dose ECG to be performed at 30 minutes (±10 minutes) post ^{64}Cu-SAR-BBN administration.
11. Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count (WBC), platelet count, differential WBC (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), absolute neutrophil count, and absolute lymphocyte count.
12. Biochemistry (pre-prandial): albumin, total protein, blood glucose, sodium, potassium, blood urea nitrogen, creatinine, calcium, uric acid, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase.
13. Coagulation: prothrombin time, activated partial thromboplastin time, D-dimer.
14. Urinalysis to include determination of protein, glucose, nitrites, and leukocytes (dipstick test).
15. If radiation or other salvage focal therapy is initiated during the study, PSA levels will be monitored independent of the study visit schedule at every 4 weeks (±2 days) from the initiation of the therapy. PSA response (defined as total PSA decline by ≥50% from baseline) must be confirmed by a second value within 4 weeks.
16. PET/CT scan to be performed at 1 to 4 hours post ^{64}Cu-SAR-BBN administration.
17. PET/CT scan to be performed at 24 hours (±6 hours) post ^{64}Cu-SAR-BBN administration.
18. Conventional imaging during screening must include an approved PSMA PET (such as ^{18}F-DCFPyL or ^{68}Ga-PSMA-11) and a CT and/or MRI. A diagnostic quality CT completed as part of a PET/CT scan is acceptable.
19. Any other available conventional imaging performed as part of routine SOC imaging workup within 60 days prior to Day 0 is to be reviewed and recorded.
20. Follow-up conventional imaging will include MRI or CT (a diagnostic quality CT completed as part of a PET/CT scan is acceptable), the same approved PSMA PET as completed at baseline. Note: Additional follow-up conventional imaging may be completed at any other timepoint, as deemed appropriate by the Investigator. All follow-up scans acquired within 180 days (±15 days) of Day 0 must be transferred to the central reading center.
21. Additional follow-up conventional imaging may be performed at the discretion of the Investigator. Where feasible, obtaining histopathology from biopsy or surgery should be attempted for as many ^{64}Cu-SAR-BBN PET-positive lesions as possible (based on the local interpretation of the ^{64}Cu-SAR-BBN PET/CT scans). If clinically feasible, the Investigator should make every effort to obtain histopathology for at least one ^{64}Cu-SAR-BBN PET-positive lesion per region. All follow-up scans and histopathology acquired within 180 days (±15 days) of Day 0 must be transferred to the central reading center.
22. Pre-SAR-BBN Disease Management Form must be completed by the treating physician to document the initial intended management plan for the participant based on available clinical information and conventional imaging results.

23. Post-SAR-BBN Disease Management Form must be completed by the treating physician for all participants who complete the ^{64}Cu-SAR-BBN PET/CT scan(s). The management plan will be based on the result from the local interpretation of the ^{64}Cu-SAR-BBN PET/CT scan(s) to document whether a change to the initial intended management plan may be warranted due to the ^{64}Cu-SAR-BBN PET/CT finding(s).