^{64}Cu-SAR-bisPSMA Positron Emission Tomography: A Phase 1/2 Study of Participants with Biochemical Recurrence of Prostate Cancer

Protocol: CLP06

STATISTICAL ANALYSIS PLAN

Version 1.0

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
^{64}Cu-SAR-bisPSMA	^{64}Copper-labelled bisCOSAR-(Lys-urea-Glu)$_2$
ADaM	analysis data model
AE	adverse event
AJCC	American Joint Committee on Cancer
ANPV	Apparent Negative Predictive Value
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
bpm	beats per minute
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
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FP	False positive
FPR	False positive rate

ICH	International Council for Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NE	non-evaluable
PC	prostate cancer
PET	Positron Emission Tomography
PP	Per Protocol
PPV	positive predictive value
PSA	prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
QT interval	the time from the start of the Q wave to the end of the T wave
QTc	corrected QT interval
QTcB	QT interval corrected using the Bazett's formula
QTcF	QT interval corrected using the Fridericia method
RR interval	the time between successive R waves
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	standard of care
SUV	Standardized uptake value
SUVr	Lesion-to-background Standardized Uptake Value Ratio
TEAE	treatment-emergent AE
TN	true negative
TNR	True negative rate
TP	true positive
ULN	upper limit of normal

WHO	World Health Organization

1.0 INTRODUCTION

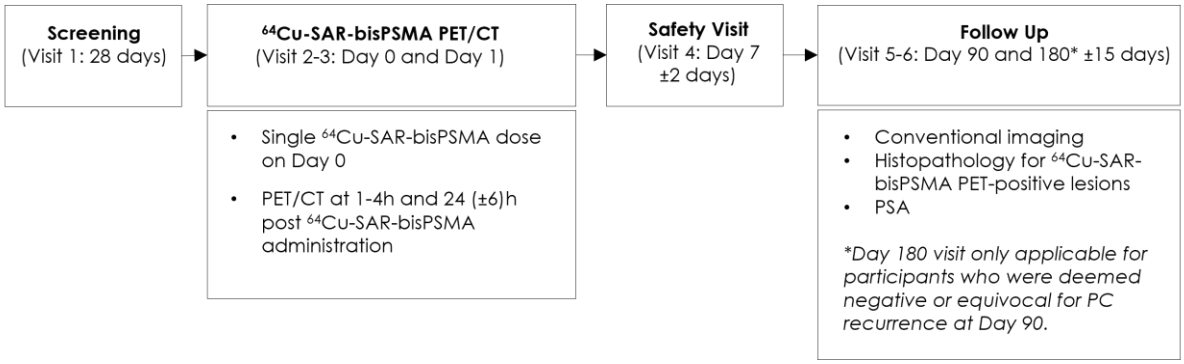
This Statistical Analysis Plan (SAP) provides the framework for the summarization and analysis of the clinical data from the "^{64}Cu-SAR-bisPSMA Positron Emission Tomography: A Phase 1/2 Study of Participants with Biochemical Recurrence of Prostate Cancer" study. Changes made to the SAP after it has been signed but prior to the database lock will be documented in an SAP amendment. Any important changes made to the analysis will be described in the Clinical Study Report (CSR).

2.0 STUDY DESIGN

This is a phase 1/2, single-arm, open-label multi-center study of ^{64}Cu-labelled SAR-bisPSMA (^{64}Cu-SAR-bisPSMA) administered to participants with biochemical recurrence of Prostate Cancer (PC) following definitive therapy. The intent is to verify the diagnostic ability of ^{64}Cu-SAR-bisPSMA.

The study consists of a single administration of ^{64}Cu-SAR-bisPSMA on Day 0, followed by a Positron Emission Tomography (PET)/Computed Tomography (CT) scan at 1 to 4 hours post dose, and at 24 hours post dose. Participants will continue to follow-up for a maximum of 180 days where the ^{64}Cu-SAR-bisPSMA PET/CT findings will be verified by follow-up conventional imaging at Day 90 and 180 (if applicable), histopathology, and Prostate-Specific Antigen (PSA) levels.

^{64}Cu-SAR-bisPSMA PET/CT scans will undergo central review by 3 blinded reviewers. 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.



3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1.1 Primary Study Objectives and Endpoints

Objective	**Endpoint**
▪ To investigate safety and tolerability of ^{64}Cu-SAR-bisPSMA.	▪ Incidence and severity of treatment-emergent adverse events (AEs) and serious AEs (SAEs) following the administration of ^{64}Cu-SAR-bisPSMA.
▪ To investigate the ability of ^{64}Cu-SAR-bisPSMA 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. ▪ 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.

3.1.2 Secondary Study Objectives and Endpoints

Objective	**Endpoint**
▪ To investigate the biodistribution of ^{64}Cu-SAR-bisPSMA.	Biodistribution of ^{64}Cu-SAR-bisPSMA 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 positive predictive value (PPV) of ^{64}Cu-SAR-bisPSMA PET/CT.	▪ Participant-level positive predictive value (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-bisPSMA PET/CT.	▪ Participant-level detection rate (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 false positive rate (FPR) ^{64}Cu-SAR-bisPSMA PET/CT.	▪ Participant-level false positive rate (FPR), defined as the proportion of 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.
▪ To assess the rate of discrepant PET negativity rate of the ^{64}Cu-SAR-bisPSMA 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 true negative rate (TNR) of ^{64}Cu-SAR-bisPSMA PET/CT.	▪ Participant-level true negative rate (TNR), defined as the proportion of 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.

3.1.3 Exploratory Study Objectives and Endpoints

Objective	**Endpoint**
▪ To evaluate the reproducibility of the ^{64}Cu-SAR-bisPSMA 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-bisPSMA 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-bisPSMA 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, PPV and DR of ^{64}Cu-SAR-bisPSMA PET/CT.	▪ CDR, participant- and region-level PPV and DR of the Day 0 and/or Day 1 scan as a function of baseline variables.
▪ To explore the correlation between ^{64}Cu-SAR-bisPSMA 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-bisPSMA 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.

4.0 HYPOTHESIS TEST AND SAMPLE SIZE ESTIMATION

4.1 Hypothesis Test

No formal hypothesis testing is planned. All statistical testing and associated p-values are presented without controlling for the alpha level.

4.2 Sample Size Estimation

Approximately 50 participants are planned to be enrolled into the study. The assumed CDR of ^{64}Cu-SAR-bisPSMA PET/CT imaging is 42% in this population. A sample size of 40 participants is estimated to provide more than 85% power to achieve a lower boundary of a 2-sided 95% exact binomial confidence interval (CI) about the estimated CDR that exceeds 20%. Accounting for a 20% non-evaluable rate, approximately 50 participants will need to undergo ^{64}Cu-SAR-bisPSMA PET/CT in this study.

Additionally, for the co-primary efficacy endpoint of region-level PPV, assuming 65% of participants are estimated to have ^{64}Cu-SAR-bisPSMA 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 34 positive regions. The assumed region-level PPV rate of ^{64}Cu-SAR-bisPSMA PET/CT imaging is approximately 65% in all PET positive regions. Therefore, a sample size of 40 participants (i.e., approximately 34 positive regions) is

estimated to provide more than 80% power to achieve a lower boundary of a 2-sided 95% exact binomial CI about the estimated region-level PPV that exceeds 40%.

5.0 RANDOMIZATION AND BLINDING

This study is single-arm so there is no randomization.

There are multiple levels of blinding present in this study for the readers involved in determining PC from various imaging modalities, creating the composite reference standard, and evaluating the ^{64}Cu-SAR-bisPSMA scans. Blinding will not be applied to the analysis as this is a single-arm study.

6.0 ANALYSIS SETS

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

Table 1 Analysis Sets

Analysis Set	Description
All Participants Set	All screened participants who signed the informed consent form. Screen failure information will be summarized using the All Participants Set.
Enrolled Analysis Set	All participants who signed the informed consent form (ICF) and were enrolled into the study. This will be used for patient disposition and analysis set summaries.
Safety Analysis Set	All enrolled participants who receive any amount of ^{64}Cu-SAR-bisPSMA. This will be used to assess safety data.
Full Analysis Set (FAS)	All participants who receive any amount of ^{64}Cu-SAR-bisPSMA and have ^{64}Cu-SAR-bisPSMA PET/CT imaging results from at least one central reader. This will be used for all efficacy analyses.
Per Protocol (PP) Analysis Set	All participants in the FAS who have an evaluable assessment of the Reference standard against ^{64}Cu-SAR-bisPSMA PET/CT imaging results for the participant-level and at least 1 region for the Day 0 and Day 1 ^{64}Cu-SAR-bisPSMA PET/CT scan and who

	have no exclusionary protocol deviations that exclude them from PP analysis. 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 have at least one biodistribution measure. This will be used to summarize biodistribution data.

7.0 STATISTICAL METHODS

7.1 General Considerations

7.1.1 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-bisPSMA administration. If an assessment has both a 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 patient at the specified time point as the value at the specified time point minus the baseline value.
- Study Day: The day of ^{64}Cu-SAR-bisPSMA administration will be on 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. Study listings will be presented as "Day 0" to match the protocol.
- For a given date, study day is calculated in the SDTM data as days since the date of single dose of ^{64}Cu-SAR-bisPSMA:
    - 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 TLF presentations as days since the date of single dose of ^{64}Cu-SAR-bisPSMA:
    - 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 according to the following formula: duration in days = (date2 – date1 + 1).

- Body Mass Index (BMI): BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2].

7.1.2 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 1 group will be reported per analysis set.

7.2 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, 25th quartile, 75th quartile, 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 number 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 patient 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.
- Version 9.4 (or higher) of the SAS® statistical software package will be used to provide all tables, listings, and figures.
- The analyses described in this plan are considered a priori, in that they have been defined prior to the first patient enrolled. Any changes to the planned analyses after first patient enrolled will be documented in this SAP and in the CSR.

7.3 Handling of Missing Data

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

7.4 Reporting Conventions

In general, the units provided for a result will mirror what is collected on the eCRF unless otherwise specified. Results collected will use the number of decimal places that are collected, with mean, SD, and median reported to 1 decimal place greater than the original data. Minimum, maximum, 25th quartile and 75th quartile values will be reported to the same number of decimal places as the collected data.

P-values will be reported to 3 decimal places, with values less than 0.001 reported as "<0.001" and values greater than 0.999 reported as ">0.999".

7.5 Replacement of Participants

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

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

7.6 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 screening #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 at baseline and during the study and require different definitions. PSA at initial diagnosis will not be used for any calculations of PSA velocity or PSADT.

For calculation of PSADT and PSA velocity at **Baseline**, which will be calculated for all participants:

- PSA Velocity = Slope of the line of best fit using all available data within 12 months prior to screening as well as screening value (excluding at initial diagnosis).
- 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 and PSA velocity for on-study measurements, only the last measure of PSA taken during the study will be used. The following calculations will be done for PSA measurements **Post-Baseline**:

- PSA Velocity = Slope of the line of best fit using all available data on-study, including screening value.
    - If the participant initiated radiation therapy on-study, the last PSA value is instead the last PSA value PRIOR to initiating radiation therapy.
- 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:

$$\overline{X} = \frac{\sum_{i=1}^{n} x_i}{n} \qquad \overline{Y} = \frac{\sum_{i=1}^{n} y_i}{n}$$

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

7.7 Imaging Scans and Reference Standard

The ^{64}Cu-SAR-bisPSMA PET/CT scans at Day 0 and Day 1 will be interpreted locally in a non-blinded fashion, and centrally by 3 different independent blinded readers in a random order. Each reader will be required to evaluate the PET/CT scans individually for the presence of pathological ^{64}Cu-SAR-bisPSMA uptake in the 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. Table 2 lists the regions and subregions that will be assessed on the ^{64}Cu-SAR-bisPSMA PET/CT scans.

Table 2 Regions and Subregions Assessed on the ^{64}Cu-SAR-bisPSMA PET/CT scans

	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	1. Lung / Pleura 2. Liver 3. Other Soft Tissue / Visceral
5	Bone	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 3 central reader interpretations will be used in the analysis. Subregion, region, and participant-level ^{64}Cu-SAR-bisPSMA status will be derived. A fourth reader may be used as a backup, and the backup reader results will replace missing reader results that they perform.

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

- A subregion is considered ^{64}Cu-SAR-bisPSMA PET/CT positive if it has at least one unequivocal PET-positive lesion.
- A region is considered ^{64}Cu-SAR-bisPSMA 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-bisPSMA PET/CT positive if they have at least one region that is considered positive.

The algorithm for determining the status of a subregion for the ^{64}Cu-SAR-bisPSMA result on Day 0 or Day 1 was changed during the study based on an amendment to the imaging database for collection of non-evaluable results for subregion-level data. This change occurred on 13-Feb-2023 and participants will be flagged in listings as to whether their ^{64}Cu-SAR-bisPSMA results were collected before or after this change.

Prior to this amendment, subregion status is defined as the following:

- A subregion is considered ^{64}Cu-SAR-bisPSMA PET/CT positive if it has at least one unequivocal PET-positive lesion.
- If a subregion has only equivocal lesions or no lesions present, the subregion is considered negative.

After this amendment, subregion status is defined as the following:

- A subregion is considered ^{64}Cu-SAR-bisPSMA PET/CT positive if it has at least one unequivocal PET-positive lesion.
- If a subregion has only equivocal lesions, the subregion is considered negative.
- 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 lesions present, the subregion is considered negative.

A reference datapoint is a follow-up histopathology assessment, PSA response, or imaging scan (with the exception of the ^{64}Cu-SAR-bisPSMA PET/CT scans) occurring between Day 1 and Day 180 that is used to confirm if PC is demonstrated on a 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 Charter.

Note: An “inconclusive” finding (as described in the protocol and imaging manuals) was 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 composite Reference Standard will be assessed against the ^{64}Cu-SAR-bisPSMA results at a region-level and a participant-level.

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

Assessment of the Reference Standard against ^{64}Cu-SAR-bisPSMA 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-bisPSMA PET/CT results separately.

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

- True Positive:
    - Histopathology: A region that is ^{64}Cu-SAR-bisPSMA 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-bisPSMA 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-bisPSMA PET-negative (no unequivocal PET-positive lesion or only equivocal lesion(s) detected within the subregions) and Reference Standard negative.
- False Positive:
    - A region that is ^{64}Cu-SAR-bisPSMA PET-positive (i.e., includes at least one unequivocal PET-positive lesion) and Reference Standard negative based on at least 1 evaluable timepoint.
- Non-evaluable:
    - A region that has either non-evaluable (NE) ^{64}Cu-SAR-bisPSMA PET/CT results for a specific timepoint (Day 0 or Day 1) or has a non-evaluable or inconclusive Reference Standard will not be assigned for that timepoint.

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

- True Positive:

  - A participant with at least one TP region and/or at least one unequivocal ^{64}Cu-SAR-bisPSMA 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 ADT is given) = total PSA decline ≥50% from baseline, confirmed by a 2nd value within 4 weeks per Prostate Cancer Working Group 3 criteria.
- True Negative:
  - A participant with a negative ^{64}Cu-SAR-bisPSMA PET/CT (i.e., no unequivocal PET-positive lesion or only equivocal 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-bisPSMA PET-positive lesion and has an evaluable Reference Standard.
- Non-evaluable:
  - A participant that has either non-evaluable ^{64}Cu-SAR-bisPSMA PET/CT results for a specific timepoint (Day 0 or Day 1) or has a non-evaluable or inconclusive Reference Standard will not be assigned for that timepoint.

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-bisPSMA imaging. For summarization purposes only, these will be considered "Test Negative" defined as a negative ^{64}Cu-SAR-bisPSMA PET/CT result within region-level or participant-level and a positive Reference Standard within region-level or participant-level.

Full programmatic details of the algorithm listed above to define ^{64}Cu-SAR-bisPSMA scan status, reference panel status, and the assessment comparing the two at the subregion-level, region-level, and participant-level will be given in a supplemental analysis document labelled: CLP06_Primary_Analysis_Supplement.xlsx.

7.9 Analysis Visit Windows for Reference Datapoints

A reference datapoint defined in the previous sections can occur at anytime post-Day 1 on study. There are 2 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:

1. The visit described in the visit form completed for the assessment will be used as the analysis visit.
2. 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:
    a. Day 90 Analysis Visit: Day 2 – Day 120 (or first analysis visit post-baseline)
    b. Day 180 Analysis Visit (only if a Day 90 already exists): Day 121 – End of Study.

8.0 DEVIATIONS FROM PROTOCOL ANALYSES

Table 3 Deviations from Protocol Analyses

Analysis Endpoint and SAP Section	Protocol v3.0 Original Analysis	Updated Analysis	Rationale
Exploratory Outcome: Function of Baseline Variables Section 9.14.3.2.	This analysis includes Lesion-to-background ratio as per protocol.	Lesion-to-background ratio not included in this exploratory analysis.	Inclusion of lesion-to-background ratio is not deemed necessary or informative in this analysis.

9.0 STATISTICAL ANALYSES

9.1 Screened Participants

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

9.2 Patient Disposition

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

- Number of patients who completed the study.

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

Patient disposition data will also be presented in listings.

9.3 Analysis Sets

Using the Enrolled analysis set, the number and percent of patients 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.

9.4 Protocol Deviations

In accordance with International Council for Harmonisation (ICH) E3, Sponsor-defined eligibility violations and important (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.

9.5 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: sex, age, 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 also be provided.

9.6 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 name.

Medical and Surgical history will be listed.

9.7 Prostate Cancer Related History

Relevant medical history related to PC will be summarized for the Safety Analysis Set, including initial prostate cancer diagnosis (PC pathology results), location of metastasis (only locations that at least 1 participant had are included), initial diagnosis stage per American Joint Committee on Cancer (AJCC) classification, initial diagnosis staging (T, N and M), initial Gleason score, 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 also be listed.

9.8 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and generic drug name 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-bisPSMA. Concomitant medications are those medications taken after the administration of ^{64}Cu-SAR-bisPSMA. As such, prior medications continued after the use of study drug are also considered concomitant medications. Prior and concomitant medications will be summarized for the Safety Analysis Set by ATC class (level 3) and preferred name. Patients receiving the same medication more than once are counted only once for each ATC class and preferred name.

All medications with partial or missing dates and times recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the administration of ^{64}Cu-SAR-bisPSMA.

Prior and concomitant medications will be listed by patient.

9.9 Cancer Surgery, Therapy, and Radiotherapy

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

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

9.10 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. Both local and central reads of these scans will be summarized and listed.

The type of imaging, modality of imaging, and recurrent PC status will be summarized as well as the results for each region and subregion, including evidence of lesions, equivocality, and number of lesions for the FAS.

Similarly, local histopathology findings will be summarized for the FAS, including the type of histopathology procedure, scan type where the lesion was identified, imaging modality used to guide biopsy (if applicable), number of lesions biopsied, number of lesions per subject with histopathology, and results for the 5 anatomical regions (PC positivity, histologic type, Gleason Score, and Gleason Grade). Central histopathology results will be summarized from the expert reference panel CRF.

Local and central SOC conventional imaging results and histopathology findings will be listed for all participants for the Enrolled Analysis Set.

9.11 Study Drug Administration

Participants will receive a single dose of ^{64}Cu-SAR-bisPSMA on Day 0. The following information will be summarized for the Safety analysis set:

- Make and model of dose calibrator.
- Reference vial activity.
- Activity in syringe before and after injection in MBq.
    - 1 mCi = 37 MBq
- Method of administration.
- Number of participants with a complete dose administered and reasons for not completely administered doses.
- Actual administered activity of ^{64}Cu-SAR-bisPSMA.

All ^{64}Cu-SAR-bisPSMA administrations will be listed with complete information from the ^{64}Cu-SAR-bisPSMA administration eCRF.

9.12 ^{64}Cu-SAR-bisPSMA PET/CT Imaging

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

For the local reader, the ^{64}Cu-SAR-bisPSMA PET/CT results (at both timepoints), the evidence of ^{64}Cu-SAR-bisPSMA uptake and number of lesions and any equivocal findings in each region/subregion will be summarized in the FAS.

All ^{64}Cu-SAR-bisPSMA PET/CT local reader data will be listed.

All central ^{64}Cu-SAR-bisPSMA PET/CT imaging results, including status and number of unequivocal lesions, will be summarized at the region-level, subregion-level, and participant-level by central reader.

All ^{64}Cu-SAR-bisPSMA PET/CT results (at both timepoints) for each central reader per participant at the subregion and region level, including lesion number, tumor state, sub-subregion, and reader comments on each lesion, will be listed.

9.13 Reference Standard

The reference standard results, as defined in Section 7.7, for the region-level, subregion-level, and participant-level will be summarized, including the level of evidence used and details surrounding the imaging, histopathology, and confirmation of PSA results that go into the final reference standard result.

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

9.14 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-bisPSMA PET/CT positive status criteria see Section 7.7 and for definitions of assessment of ^{64}Cu-SAR-bisPSMA results against the Reference Standard results, see Section 7.8. Alpha level is set to 0.05 for all p-values but alpha is not controlled, and p-values are considered exploratory.

All analyses that are considered “region-level” will be conducted in 2 ways (unless otherwise specified): the analysis will be conducted on all 5 regions as a whole (labeled as “All Regions”) and by-region individually, for 6 total calculations.

9.14.1 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 1 evaluable reference standard datapoint collected and is calculated as: CDR = TP/(all scanned participants with at least 1 evaluable reference datapoint) x 100.

Participants without a ^{64}Cu-SAR-bisPSMA 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 (the primary endpoint will be calculated including all 5 regions as a whole) for each central reader and is defined as the proportion of TP regions out of all positive regions on the ^{64}Cu-SAR-bisPSMA PET/CT scan with corresponding evaluable composite Reference Standard data and will be calculated as: PPV = TP/(TP + FP) x 100, where FP = False Positive.

Regions that are not positive on the ^{64}Cu-SAR-bisPSMA 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
    - This region is incorrectly labeled as Region 5 in the raw data and will be recoded
- Region 5 = Bone
    - 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 1 reference datapoint, and 2-sided 95% exact binomial confidence intervals (CI) using the Clopper-Pearson method. All primary endpoints will be summarized for the FAS (noting that subjects within the FAS without sufficient results to construct the required outcome variable for the endpoint [e.g. a participant without and 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 displaying the participant-level CDR and region-level PPV by central reader at Day 0 and Day 1 in the FAS analysis set.

9.14.1.1 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 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 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.
  - $p = 0$ corresponds to none of the participants in the Reference Standard with missing data will be imputed as TP while $p = 1$ corresponds to all participants in the Reference Standard with missing data will be imputed as TP.
  - 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 same way as the primary analysis for CDR and PPV for Day 0 and 1 without 95% CI.
  - Figures displaying the CDR or PPV curve of point estimates for each value of p will be presented.

9.14.2 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% CI in the FAS and repeated with the PP analysis set:

- Participant-level PPV at Day 0 and Day 1;
  - PPV = TP/(TP + FP) x 100.
- Participant-level Detection Rate (DR) at Day 0 and Day 1;
  - DR = (number of participants with positive ^{64}Cu-SAR-bisPSMA PET/CT scan)/(all scanned participants with a ^{64}Cu-SAR-bisPSMA PET/CT scan) x 100.

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

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

9.14.3 Exploratory Efficacy Analyses

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

9.14.3.1 Composite ^{64}Cu-SAR-bisPSMA 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-bisPSMA PET/CT scan if they meet one of the following criteria:

- A positive ^{64}Cu-SAR-bisPSMA result on both Day 0 and Day 1.
- A positive ^{64}Cu-SAR-bisPSMA result on Day 0 and negative, missing, or equivocal ^{64}Cu-SAR-bisPSMA result on Day 1.
- A negative, missing, or equivocal ^{64}Cu-SAR-bisPSMA result on Day 0 and a positive ^{64}Cu-SAR-bisPSMA 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-bisPSMA PET/CT scan on both Day 0 and Day 1.

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

9.14.3.2 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): <3.0, 3.0-8.9, 9.0-14.9, ≥15.0 months.
- PSA velocity at baseline: 0 to <0.05, 0.05 to <0.10, 0.10 to <0.20, ≥0.20 ng/mL/y.
- Testosterone at baseline: <230, 230-350, >350 ng/dl.
- Standardized uptake value (SUV) max: ≤2, 2-<5, 5-<10, ≥10.
- Initial treatment received (2 categories): radical prostatectomy OR radiation therapy, cryotherapy and brachytherapy.
- 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 = imaging results (regardless of PSA response being available) but no contributing histopathology information,

  - Level 3 = PSA response only ((i.e., no contribution of histopathology or imaging result information (participant-level only)).
- Size of largest lesion (long axis) identified on ^{64}Cu-SAR-bisPSMA PET/CT central reader scan: 0 - <0.5, 0.5 - <1.0, ≥1.0 cm.
- Time to ^{64}Cu-SAR-bisPSMA 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 baseline categorical variables with CDR, PPV, and DR values in each category by central reader. Region-level parameters will only be summarized for the "All regions" category and not the individual regions.

9.14.3.3 PET-positivity versus True/False Positivity

Biodistribution parameters in lesions and organs as percentage of mean and max SUV in all lesions, visceral/soft tissue lesions, and bone lesions, lesion-to-background ratio, and lesions size will be used to explore the proportion of participants with participant-level TP and FP at Day 0 and Day 1 by central reader in the Biodistribution Analysis Set. For the summarization of lesions, the mean of the lesions within a participant will be used for the definition.

Biodistribution variables and lesions size will be compared individually between TP vs. FP groups using a Wilcoxon rank sum test at a region-level.

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

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

The total number of, and difference in, the number of lesions detected per participant on the Day 0 and Day 1 ^{64}Cu-SAR-bisPSMA PET/CT scans will be summarized descriptively by central reader. The number of lesions on Day 0 and Day 1 will be compared using a Wilcoxon signed rank test, with the test p-value and median difference summarized by central reader.

Additionally, the number of positive regions detected per participant on the Day 0 and Day 1 ^{64}Cu-SAR-bisPSMA PET/CT scans will be summarized descriptively by central reader. The number of positive regions on Day 0 and Day 1 will be compared using a chi-square test, with the test p-value presented by central reader.

9.14.3.5 Lesion-level Overall Agreement

The following scans will be assessed for overall lesion-level agreement rate per scan type (i.e., bone scan, CT, MRI, PSMA PET, etc.):

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

9.14.3.6 PSA Measures Change from Baseline

Total PSA, PSA velocity, and PSADT levels 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 levels 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, and PSADT levels will be listed.

9.14.4 Intra and Inter-reader Variability

9.14.4.1 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-bisPSMA 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 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-bisPSMA 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-bisPSMA 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), 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 interpretations of Cohen's kappa are presented in Table 4.

Table 4 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 data points as the first, original evaluation. The following variables will be assessed for intra-reader variability:

- Participant and region-level ^{64}Cu-SAR-bisPSMA PET/CT positivity described in the Primary Endpoint analysis
- Average number of positive lesions at participant and region-level

9.14.4.2 Inter-reader Variability

For dichotomous results of ^{64}Cu-SAR-bisPSMA 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-bisPSMA 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-bisPSMA 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, Pearson interclass correlations (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-bisPSMA PET/CT positivity
- Number of positive lesions at participant and region-level

9.14.5 Disease Management

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

The proportion of participants with any change in intended PC treatment due to either Day 0, Day 1, both, and sum of participants who had change due to a ^{64}Cu-SAR-bisPSMA scans will be summarized, with binomial Clopper-Pearson 95% CI.

All disease management data for both timepoints will be listed.

9.15 Safety Analyses

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

9.15.1 Adverse Events

AEs will be coded to system organ class and preferred term according to MedDRA, version 25. Pretreatment 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 first dose of study drug. Treatment-emergent adverse events (TEAEs) are defined as AEs that start or worsen after the first dose of ^{64}Cu-SAR-bisPSMA.

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 dose of ^{64}Cu-SAR-bisPSMA or a stop date indicates the AE ended before the dose of ^{64}Cu-SAR-bisPSMA.

Summaries will be provided for TEAEs, with the number and percentage of participants reporting each type of event presented. If a participant's reports 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 patient only counts once for that system organ class. Furthermore, for a given summary, the preferred term will only be counted once at its worst severity and strongest relationship to study drug.

PC symptoms of special interest will be collected and summarized separately by body system.

The following summaries and listings for AEs will be provided:

- An overall summary table of AEs summarizing the number and percent of patients, in the following categories: any AE, any TEAE, TEAEs by highest severity grade, TEAEs by relationship to study drug (related, not related), any serious TEAE, TEAEs leading to discontinuation from the study, TEAEs leading to study drug withdrawal, any TEAEs with a fatal outcome.
- Incidence of TEAEs by MedDRA system organ class and preferred terms.
- Incidence of TEAEs by MedDRA system organ class, preferred terms, and maximum severity grade.
- Incidence of 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 related TEAEs grade 3 or higher by MedDRA system organ class and preferred term.
- Incidence of Serious Adverse Events by MedDRA system organ class and preferred term.

- Incidence of related Serious Adverse Events by MedDRA system organ class and preferred term
- Listing of all AEs (with non-treatment-emergent events flagged).
- Listing of all AEs for patients who withdrew from study or study drug due to an AE.
- Listing of all SAEs.

9.15.2 Clinical Laboratory Evaluations

Descriptive statistics for chemistry, hematology, coagulation, urinalysis, eGFR (categorized as chemistry), and serum testosterone and the change from baseline will be summarized for the Safety Analysis Set at each scheduled time point.

Laboratory values will be categorized into normal or higher or lower than the normal range. Laboratory values will be presented in standard international (SI) units. Number and percent of participants with abnormal laboratory values will be summarized by timepoint. Shift tables based on CTCAE v5.0 toxicity grading as shown in Appendix 2 will be provided for shifts from baseline to the highest and lowest post-baseline grade. Shift tables will be presented for hematology, chemistry, coagulation, and urinalysis parameters as applicable.

Listings will be provided by participant and study visit. Values for all safety laboratory results that are outside the laboratory reference ranges will be flagged on the individual patient data listings as high or low. Additionally, listings of abnormal laboratory values will be provided.

9.15.3 Vital Signs

Systolic and diastolic blood pressures (mmHg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C), as well as height, weight, and BMI, will be summarized using descriptive statistics at all scheduled time points. Descriptive statistics of the change from baseline to each post-baseline time point will also be provided.

9.15.4 Electrocardiogram (ECG) Parameters

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

The values of the ECG parameters: RR interval, PR interval, QRS interval, QT interval, QTcB, and QTcF interval will be summarized using descriptive statistics at all scheduled time points as well as changes from baseline. Shift tables will be provided for changes from baseline 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 greatest clinical significance will be used for the shift table category assignment.

The number and percentages of participants with QTcF and QTcB values that fall into the following categories post-baseline will also be summarized:

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

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

- <0 msec
- 0 - 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.

9.15.5 Physical Examination

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

9.15.6 Prostate Cancer Symptoms

PC symptoms will be summarized by body system, symptom, and severity grade for the Safety Analysis Set. Locations of symptoms will also be summarized.

All PC symptom data will be listed.

9.16 Biodistribution Analysis

For the Biodistribution Analysis Set, biodistribution measures for ^{64}Cu-SAR-bisPSMA of mean and max SUV, lesion longest diameter, lesion longest perpendicular, lesion-to-background ratios (SUVr), and reader confidence levels will be summarized descriptively. Mean and max SUV will use the mean of all lesions within a participant to summarize SUV in all lesions, and separately will summarize mean and max SUV in lesions in visceral/soft tissues and lesions in bone. Similarly, lesion-to-background ratio will use the mean values of the lesions within a participant. Boxplots will be provided for the biodistribution measures.

Additional summaries the of biodistribution measures 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 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. Reader confidence levels will also be listed.

APPENDICES

Appendix 1 Schedule of Events

	Screening[1]	**^{64}Cu-SAR-bisPSMA 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-bisPSMA Dose		X					
^{64}Cu-SAR-bisPSMA PET/CT			X[16]	X[17]			
SOC Conventional Scan	X						
Follow-up Conventional Imaging[18]						X	X
Additional Imaging/Histopathology[19]					X		

Disease Management Form	X[20]				X[21]		

[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. Institutional SOC scan(s) must be performed within 60 days of Day 0. SOC 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-bisPSMA 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-bisPSMA PET/CT.

[10] Post-dose ECG to be performed at 30 minutes (±10 minutes) post ^{64}Cu-SAR-bisPSMA administration.

[11] Hematology: hemoglobin, hematocrit, red 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, AST, ALT, total bilirubin, alkaline phosphatase.

[13] Coagulation: prothrombin time, activated partial thromboplastin time, D-dimer.

[14] Urinalysis to include determination of protein, glucose 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-bisPSMA administration. If no anatomical imaging (CT or MRI) is available within 60 days of Day 0, a diagnostic quality CT must be acquired as part of the Day 0 PET/CT scan.

[17] PET/CT scan to be performed at 24 hours (±6 hours) post ^{64}Cu-SAR-bisPSMA administration.

[18] Follow-up conventional imaging will include MRI or CT (a diagnostic quality CT completed as part of a PET/CT scan is acceptable) and ^{99m}Tc-MDP and/or ^{18}F-fluciclovine and/or ^{11}C-choline and/or approved PSMA PET (such as ^{18}F-DCFPyL or ^{68}Ga-PSMA-11). *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.*

[19] 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-bisPSMA PET-positive lesions as possible (based on the local interpretation of the ^{64}Cu-SAR-bisPSMA PET/CT scans). If clinically feasible, the Investigator should make every effort to obtain histopathology for at least one ^{64}Cu-SAR-bisPSMA 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.

[20] Pre-SAR-bisPSMA 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.

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

Appendix 2 Programmatic CTCAE v5.0 Toxicity Grading

Laboratory Test/Vital Sign	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry				
(Albumin) Hypoalbuminemia	<LLN – 3 g/dL; <LLN – 30 g/L	<3-2 g/dL; <30-20 g/L	<2 g/dL; <20 g/L	
Alkaline phosphatase increased	>ULN – 2.5 x ULN if baseline was normal; 2.0-2.5 x baseline if baseline was abnormal	>2.5 – 5.0 x ULN if baseline was normal; >2.5-5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0-20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alanine aminotransferase (ALT) increased	>ULN – 3 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0-5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0-20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase (AST) increased	>ULN – 3 x ULN if baseline was normal; 1.5-3.0 x baseline if baseline was abnormal	>3.0 – 5.0 x ULN if baseline was normal; >3.0-5.0 x baseline if baseline was abnormal	>5.0 – 20.0 x ULN if baseline was normal; >5.0-20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
(Calcium high, corrected) Hypercalcemia	>ULN – 11.5 mg/dL; >ULN – 2.0 mmol/L	>11.5 – 12.5 mg/dL; >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL; >3.1 – 3.4 mmol/L	>13.5 mg/dL; >3.4 mmol/L;
(Calcium low, corrected) Hypocalcemia	<LLN – 8.0 mg/dL; <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL; <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL; <1.75 – 1.5 mmol/L Hospitalization	<6.0 mg/dL; <1.5 mmol/L Life-threatening

Laboratory Test/Vital Sign	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine Increased	>ULN – 1.5 ULN	>1.5 – 3.0 x baseline >1.5-3.0 x ULN	>3.0 x baseline >3.0-6.0 x ULN	>6.0 x ULN
(eGFR or Creatinine Clearance) Chronic Kidney Disease	eGFR or CrCL < LLN – 60 ml/min/1.73 m2	eGFR or CrCl 59 – 30 ml/min/1.73 m2	eGFR or CrCl 29 -15 ml/min/1.73 m2	eGFR or CrCl < 15 ml/min/1.73 m2
(Glucose) Hypoglycemia	<LLN – 55 mg /dL; <LLN – 3.0 mmol/L	<55 – 40 mg/dL; <3.0 – 2.2 mmom/L	<40 – 30 mg/dL; <2.2 – 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; Life-threatening
(Potassium high) Hyperkalemia	>ULN – 5.5 mmol/L	>5.5 - 6.0 mmol/L; *intervention initiated*	>6.0-7.0 mmol/L; Hospitalization	>7.0 mmol/L; Life-threatening
(Potassium low) Hypokalemia		<LLN – 3.0 mmol/L	<3.0 – 2.5 mmol/L; Hospitalization	<2.5 mmol/L; Life-threatening
(Sodium high) Hypernatremia	>ULN – 150 mmol/L	>150-155 mmol/L	>155-160 mmol/L; Hospitalization	>160 mmol/L; Life-threatening
(Sodium low) Hyponatremia	<LLN – 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L
Total bilirubin increased	>ULN – 1.5 x ULN if baseline was normal; 1.0-1.5 x baseline if baseline was abnormal	>1.5 – 3.0 x ULN if baseline was normal; >1.5-3.0 x baseline if baseline was abnormal	>3.0 – 10.0 x ULN if baseline was normal; >3.0-10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Hematology				
Hemoglobin increased	Increase in >0-2 g/dL	Increase in >2-4 g/dL	Increase in >4 g/dL	
(Hemoglobin low)	<LLN – 10.0 g/dL	<10.0-8.0 g/dL	<8.0 g/dL	

Laboratory Test/Vital Sign	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anemia	<LLN – 6.2 mmol/L <LLN – 100 g/L	<6.2-4.9 mmol/L <100-80 g/L	<4.9 mmol/L <80 g/L	
Lymphocyte count decreased	<LLN – 800/mm3 <LLN – 0.8 x 10^9/L	<800-500/mm3 <0.8-0.5 x 10^9/L	<500-200/mm3 <0.5-0.2 x 10^9/L	<200/mm3 <0.2 x 10^9/L
Lymphocyte count increased		>4000/mm3-20,000/mm3	>20,000/mm3	
Neutrophil count decreased	<LLN – 1500/mm3 <LLN – 1.5 x 10^9/L	<1500 - 1000/mm3 <1.5-1.0 x 10^9/L	<1000 - 500/mm3 <1.0-0.5 x 10^9/L	<500/mm3 <0.5 x 10^9/L
Platelet count decreased	<LLN – 75,000/mm3 <LLN – 75.0 x 10^9/L	<75,000 - 50,000/mm3 <75.0-50.0 x 10^9/L	<50,000 - 25,000/mm3 <50.0 – 25.0 x 10^9/L	<25,000/mm3 <25.0 x 10^9/L
WBC Count decreased	<LLN – 3000/mm3 <LLN-3.0 x 10^9/L	<3000-2000/mm3 <3.0-2.0 x 10^9/L	<2000-1000/mm3 <2.0-1.0 x 10^9/L	<1000/mm3 <1.0 x 10^9/L
Coagulation				
aPTT/PTT prolonged	>ULN – 1.5 x ULN	>1.5 – 2.5 x ULN	>2.5 x ULN	
Urinalysis				
(Protein high) Proteinuria	1+ proteinuria; Urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; Urinary protein 1.0 - <3.5 g/24 hrs;	4+ proteinuria; Urinary protein >=3.5 g/24 hrs;	