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

Protocol: CLB03

CLINICAL STUDY PROTOCOL

Version 2.0

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Clarity Pharmaceuticals Ltd

CLINICAL STUDY PROTOCOL: CLB03

Title:	^{64}Cu-SAR-BBN Positron Emission Tomography: A Phase 2 Study of Participants with PSMA-negative Biochemical Recurrence of Prostate Cancer
Short Title:	**SABRE** (Copper-64 **SA**R-BBN in **B**iochemical **RE**currence of Prostate Cancer)
Investigational Product:	^{64}Cu-SAR-BBN
Protocol No.:	CLB03
Sponsor:	Clarity Pharmaceuticals Ltd. National Innovation Centre 4 Cornwallis St, Eveleigh NSW 2015 Australia Telephone: +61 2 9209 4037
IND No.:	161210
Phase:	Phase 2
Medical Monitor:	[redacted]
Protocol Version (Date):	2.0 (27-Feb-2023)
Previous Version(s) of the Protocol:	1.0 (28-Apr-2022)

Confidentiality Statement

SPONSOR PROTOCOL APPROVAL

Protocol Title:	^{64}Cu-SAR-BBN Positron Emission Tomography: A Phase 2 Study of Participants with PSMA-negative Biochemical Recurrence of Prostate Cancer
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This version of the clinical protocol has been approved by Clarity Pharmaceuticals Ltd.

[redacted]

Date

[redacted]

Clarity Pharmaceuticals Ltd

PROTOCOL SYNOPSIS

Protocol Number	CLB03
Investigational Product	^{64}Cu-SAR-BBN
Protocol Title	^{64}Cu-SAR-BBN Positron Emission Tomography: A Phase 2 Study of Participants with PSMA-negative Biochemical Recurrence of Prostate Cancer
Short Title	**SABRE** (Copper-64 **SA**R-BBN in **B**iochemical **RE**currence of Prostate Cancer)
Phase	2
IND Number	161210
Study Sponsor	Clarity Pharmaceuticals Ltd.
Study Centers Planned	Multi-center
Study Design	This is a 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. The maximum Screening period for each participant is 28 days. After the Screening period, eligible participants will receive a single administration of ^{64}Cu-SAR-BBN on Day 0, followed by a positron emission tomography (PET)/computed tomography (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 maximum Follow-up period for each participant is 180 days. 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.

Primary Study Objectives and Endpoints

Objective	Endpoint
To investigate the safety and tolerability of ^{64}Cu-SAR-BBN.	Incidence and severity of treatment-emergent AEs and 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 CDR, defined as the proportion of 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 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.

Abbreviations: AE= adverse event; CDR= correct detection rate; CT= Computed Tomography; PET= Positron Emission Tomography; PC= prostate cancer; PPV= positive predictive value; SAE= serious adverse event; TP= true positive

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 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 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 FPR ^{64}Cu-SAR-BBN PET/CT.	• Participant-level 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 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 TNR of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level 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.

Abbreviations: CT= computed tomography; DR= detection rate; FP= false positive; FPR= rate of false positive; PET= positron emission tomography; PPV= positive predictive value; SUV= standardized uptake value; TN= true negative; TNR= rate of true negative; TP= true positive

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, PPV and DR of ^{64}Cu-SAR-BBN 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-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.

Abbreviations: CDR= correct detection rate; CT= computed tomography; DR= detection rate; PC= prostate cancer; PET= positron emission tomography; PPV= positive predictive value; TP = true positive

Number of Participants Planned	50
Target Population	Biochemical recurrence of PC following definitive therapy with negative or equivocal PC findings on approved PSMA PET and anatomical imaging (CT and/or MRI), and other conventional imaging, if available.
Inclusion Criteria	Study candidates must meet <u>all</u> the following criteria to be eligible for the study: 1. At least 18 years of age; 2. Signed informed consent; 3. Life expectancy ≥ 12 weeks as determined by the Investigator. 4. Histologically confirmed adenocarcinoma of prostate per original diagnosis and completed subsequent definitive therapy. 5. Suspected recurrence of PC based on rising PSA after definitive therapy on the basis of: a. Post-radical prostatectomy: detectable or rising PSA that is ≥ 0.2 ng/mL with a confirmatory PSA ≥ 0.2 ng/mL (per American Urological Association recommendation); or b. Post-radiation therapy, cryotherapy, or brachytherapy: increase in PSA level that is elevated by ≥ 2 ng/mL above the nadir (per American Society for Therapeutic Radiology and Oncology-Phoenix consensus definition). 6. Negative or equivocal findings for PC on (1) approved PSMA PET and (2) anatomical imaging (CT and/or magnetic resonance imaging) and (3) if available, any other conventional imaging performed as part of routine standard of care imaging workup within 60 days prior to Day 0. 7. The Eastern Cooperative Oncology Group performance status 0-2.

	8. Adequate recovery from acute toxic effects of any prior therapy. 9. Estimated Glomerular Filtration Rate of 30 mL/min or higher. 10. Adequate liver function defined as alanine aminotransferase/aspartate aminotransferase <3 x upper limit of normal (ULN) and total bilirubin <1.5 x ULN (except in the case of Gilbert's syndrome). 11. For participants who have partners of childbearing potential: Partner and/or participant must use a method of birth control with adequate barrier protection.
Exclusion Criteria	Study candidates who meet <u>any</u> of the following criteria are not to be enrolled in the study: 1. Participants who received other investigational agents within 28 days prior to Day 0. 2. Participants administered any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives prior to Day 0. 3. Ongoing treatment or treatment within 90 days of Day 0 with any systemic therapy (e.g., androgen-deprivation therapy, antiandrogen, gonadotropin-releasing hormone, luteinizing hormone-releasing hormone agonist or antagonist) for PC. 4. Participants who are known to require prohibited treatment (e.g., initiation of androgen-deprivation therapy due to rapidly rising PSA) before the ^{64}Cu-SAR-BBN PET/CT results can be verified via histopathology or follow-up imaging. 5. Known or expected hypersensitivity to ^{64}Cu-SAR-BBN or any of its components. 6. Any serious medical condition or extenuating circumstance which the Investigator feels may interfere with the procedures or evaluations of the study.
Investigational Product, Dose, and Regimen	The investigational product administered in this study is ^{64}Cu-SAR-BBN. ^{64}Cu-SAR-BBN has 3 basic components; the radionuclide (^{64}Cu) bound via MeCOSar (a bifunctional metal chelator) to an antagonist that targets Gastrin Releasing Peptide Receptor.
Statistical Methods	A Statistical Analysis Plan (SAP) will be written after finalizing the protocol and prior to database lock. The SAP will detail the implementation of all the planned statistical analysis in accordance with the principal features stated in the protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
^{18}F	fluorine-18
^{18}F-FACBC	^{18}F-fluciclovine; registered as Axumin®
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{18}F-NaF	^{18}F-sodium fluoride
^{64}Cu	copper-64
^{64}Cu-SAR-BBN	^{64}Cu-labeled SAR-BBN
^{67}Cu	copper-67
^{68}Ga	gallium-68
^{68}Ga-RM2	gallium-68-labeled GRPR targeting agent
^{99m}Tc-MDP	^{99m}Tc-methylene diphosphonate
ADT	androgen-deprivation therapy
AE	adverse event
CDR	correct detection rate
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
^{nat}Cu-SAR-BBN	Natural copper-labeled SAR-BBN
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DICOM	Digital Imaging and Communications in Medicine
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDT	electronic data capture
eGFR	estimated Glomerular Filtration Rate
FAS	full analysis set
FDA	Food and Drug Administration
FP	false positive
GCP	Good Clinical Practice
GRP	gastrin releasing peptide
GRPR	gastrin releasing peptide receptor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	institutional review board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
^{nat}Cu	natural stable Cu

Abbreviation/Term	Definition
NCI	National Cancer Institute
PC	prostate cancer
PET	positron emission tomography
PPV	positive predictive value
ProstaScint®	^{111}In-labeled-capromab-pendetide
PSA	prostate-specific antigen
PSADT	PSA doubling time
PSMA	prostate specific membrane antigen
SAE	serious adverse event
SAP	statistical analysis plan
SAR-BBN	MeCOSar-PEG4-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2
SOC	standard of care
SUV	standardized uptake value
$t_{1/2}$	half-life
TEAE	treatment emergent adverse event
TN	true negative
TP	true positive
ULN	upper limit of normal
USA	United States of America
WBC	white blood cells count

AMENDMENT 1 (V2.0, 27-FEB-2023)

Amendment rationale and summary of changes:

The purpose of this amendment is to address recommendations provided by Investigators, to provide clarifications on study assessments, analyses of data and to address minor typographical errors.

Summary of Changes	
Section Reference Version 2.0, 27-FEB-2023	**Amendment Description**
Throughout the protocol	Version and date of the document has been updated.
Throughout the protocol	Typographical, formatting corrections, administrative changes, and text clarifications.
Section 4.1, Section 7.3, Table 5, Section 8.2.7, Section 8.6.1, Section 8.6.2	List of prohibited treatments amended to allow for any focal salvage therapy. PSA response following any focal salvage therapy is to be monitored every 4 weeks from the initiation of any salvage focal therapy (in the same way as after radiation therapy). Histopathological confirmation of PC prior to commencement of radiation or other salvage focal therapy is strongly encouraged.
Section 4.1, Section 8.4, Table 5	Clarification added regarding histopathology requirements: 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.
Section 5.1.2	Exclusion criteria added: Participants who are known to require prohibited treatment (e.g., initiation of ADT due to rapidly rising PSA) before the ^{64}Cu-SAR-BBN PET/CT results can be verified via histopathology or follow-up imaging.
Section 5.4.4	Clarification included regarding the participant replacement criteria: 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.
Section 7	Note added: Participants who are known to require prohibited treatment (e.g., initiation of ADT due to rapidly rising PSA) before the ^{64}Cu-SAR-BBN PET/CT results can be verified via histopathology or follow-up imaging should not be considered for participation in this study.
Section 7.3	Clarification added: Participants who receive prohibited treatment(s) should remain in the study until completion of Visit 4.
Section 8.2.6	Removal of the note referencing assessment of triglycerides. Clarification added regarding assessment of significance for abnormal PSA values.
Section 8.3.2.2	Definition included for equivocal ^{64}Cu-SAR-BBN PET-lesions.
Section 8.4	Removal of the requirement for the local pathologist evaluating samples to be blinded to the ^{64}Cu-SAR-BBN PET/CT results.
Section 8.6.1	Region- and subregion-level requirements for a positive Reference Standard status included.
Section 8.6.1, Section 8.6.2	Handling of equivocal / unequivocal lesions and non-evaluable and inconclusive results in the analyses was clarified. Clarification included regarding the process of matching of the Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results.
Section 11.4.5, Section 11.6	Clarification of the CDR endpoint calculation and requirements for reference standard datapoints added. Participants with non-evaluable

Summary of Changes	
Section Reference Version 2.0, 27-FEB-2023	**Amendment Description**
	participant-level Reference Standard results will be excluded from the CDR calculation. Removal of non-evaluable regions from the analysis of region-level PPV endpoint. PET/CT positive regions without corresponding evaluable composite Reference Standard results will no longer be included in the denominator for the region-level PPV calculation. Removal of the sensitivity analyses of the participant-level CDR and region-level PPV based on participants in the full analysis set who had evaluable composite Reference Standard results.
Section 11.4.5.3	Assessment of CDR, PPV and DR as a function of anatomic region removed.

Abbreviations: ADT= androgen-deprivation therapy, CDR= correct detection rate, CT= computed tomography, DR= detection rate, PET= positron emission tomography, PPV= positive predictive value, PSA= prostate-specific antigen.

1 INVESTIGATIONAL TEAM

Refer to the trial specific contact list for details of investigators, sponsor personnel, clinical research organisation personnel and facilities used in the study.

2 INTRODUCTION

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2.1 Background

Prostate cancer (PC) is the second most frequent malignancy in men[1]. The American Cancer Society estimates 248,530 new cases of PC were diagnosed in the United States of America (USA) in 2021 accounting for approximately 25% of all new estimated cancer cases in men and approximately 13% of all new estimated cancer cases[2,3]. The incidence of PC correlates with age, running between 30% for patients 40-50 years old to 50-80% for patients aged 80 and over[4]. Median age at diagnosis is 67 years and median age at death is 81 years[5,6]. Although the etiology of the disease is unclear, the main risk factors include advanced age, ethnicity, and positive family history[7]. While some patients with PC have indolent disease, where the patient's serum prostate-specific antigen (PSA) values are followed without further treatment, the majority of patients will receive some treatment for their PC. Between 20-40% of patients with PC will relapse within 10 years of their primary PC treatment, as identified through rising PSA levels. At relapse, approximately 25-35% of patients have locally recurrent disease, 20-25% have metastatic disease, and 45-55% have both local and metastatic disease[8]. As disease extent determines the treatment, accurate staging and re-staging particularly in early biochemical recurrence are imperative for optimizing treatment regimes.

Gastrin Releasing Peptide Receptor (GRPR) is a transmembrane G-protein coupled receptor that has various physiological functions in the gastrointestinal tract and nervous system[9]. Its pharmacological activities, through binding of its ligand Gastrin Releasing Peptide (GRP), include the stimulation of hormone releasing, like gastrin and somatostatin, as well as stomach and intestine smooth muscle contraction. Gastrin Releasing Peptide Receptor expression is upregulated in many human cancers[10], including PC[11,12] and breast cancer[13], with its normal biodistribution mainly concentrated in the pancreas and gastrointestinal tract. Although the correlation between GRPR expression and clinical features in PC, such as Gleason score, stage of disease and PSA levels, have been evaluated, the results remain inconclusive[10]. Indeed, a recent study showed uptake of a gallium-68-labeled GRPR targeting agent (^{68}Ga-RM2) across all PSA levels in biochemical recurrent PC[14].

The Sponsor is developing a radiolabeled antagonist of GRPR for the diagnosis and management of PC. The product is copper-64-labeled MeCOSar-PEG$_4$-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2 (^{64}Cu-SAR-BBN). ^{64}Cu-SAR-BBN uses a radioactive form (radionuclide) of copper, Copper-64 (^{64}Cu) to image cancers using Positron Emission Tomography (PET).

The target population for this study is patients with biochemical recurrence of PC following initial definitive therapy. Although PSA is the primary biomarker for recurrence, it does not reflect the location or the extent of disease recurrence. Despite recent advances in imaging techniques, some patients will fail to have their recurrence accurately localized by imaging, especially at low PSA levels. Identifying tumor relapses and metastases is challenging for conventional imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) due to limitations in sensitivity and specificity. Early diagnosis of recurrence and accurate staging are essential to inform the best treatment strategy. Prostate Specific Membrane Antigen (PSMA)-targeting PET agents have been shown to have superior sensitivity and specificity compared to conventional imaging, with frequent identification of

sub-centimeter PC lesions. Although a PSMA-targeting PET scans is effective for imaging disease in the prostate, lymph nodes, soft tissue, and bone in a single examination[15], the overexpression of PSMA in PC is not universal and 21% of biochemical recurrent PC patients were found to have no lesions with characteristics of recurrent PC detected on their PSMA PET scan[16]. Studies comparing GRPR- and PSMA-targeting PET highlighted a distinct distribution of the two targets in biochemically recurrent PC[14,17], suggesting GRPR-targeting PET may add diagnostic value in PSMA-negative PC patients.

Refer to the Investigator's Brochure (IB) for detailed information on ^{64}Cu-SAR-BBN.

2.2 Imaging of Prostate Cancer

Conventional imaging modalities such as MRI, CT, and ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scan, suffer from limited sensitivity and specificity, which can result in inaccurate disease staging leading to suboptimal treatment. The use of molecular imaging using PET has therefore been explored to better identify sites of disease. A number of new PET diagnostic radiopharmaceuticals have emerged in recent years, including agents that accumulate on the basis of alterations in cellular metabolism as well as those that bind to specific proteins, such as PSMA[18].

Approved diagnostic radiopharmaceuticals that are commonly used to image PC include ^{99m}Tc-MDP bone scan, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-sodium fluoride (^{18}F-NaF), ^{11}C-choline, ^{18}F-FACBC (or ^{18}F-fluciclovine; registered as Axumin®), and more recently, PSMA-based PET radiopharmaceuticals, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (registered as PYLARIFY®)[18,19].

Currently, ^{99m}Tc-MDP planar whole-body scanning is the imaging standard for detection of osseous metastases. The ^{18}F-NaF uptake mechanism in the bone is similar to that for ^{99m}Tc-MDP but with better sensitivity and specificity in the detection of bone metastases. These scans are both lacking in specificity however, with uptake in areas of bone remodeling such as infection and trauma, in addition to osseous metastases. Furthermore, they are limited in the detection of soft-tissue malignancies, including the primary tumor, lymph node disease, and visceral metastases.

Although molecular imaging in oncology is most commonly performed with ^{18}F-FDG PET, this test has not shown clinical utility in PC imaging[20]. PC cells typically do not undergo increased aerobic glycolysis, limiting the use of ^{18}F-FDG. These cells do, however, display upregulated de novo lipid synthesis and activity of lipogenic enzymes. This enables lipid precursors such as choline to function as radiotracers for PET imaging in PC. ^{11}C-choline was approved by the Food and Drug Administration (FDA) in 2012, but choline-based radiotracers are not cancer specific, and can be taken up in other tissues or areas of benign inflammation. In addition, its use is affected by the short half-life ($t_{1/2}$=20 minutes). In studies comparing ^{11}C-choline to ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-11 showed a higher detection rate than ^{11}C-choline PET for lymph nodes as well as bone lesions[21,22]. ^{18}F-FACBC targets multiple sodium-dependent and independent channels which are upregulated in PC. ^{18}F-FACBC is a synthetic amino acid that is well tolerated and able to detect local and distant PC recurrences across a wide range of PSA values[23]. However, like ^{11}C-choline, ^{18}F-FACBC was shown to be inferior to ^{68}Ga-PSMA-11 in prospective imaging trials[24].

Prostate specific membrane antigen has been studied extensively as an imaging target in PC. The first commercialized PSMA targeting imaging agent was ^{111}In-labeled-capromab-pendetide (ProstaScint®), which was approved by the FDA in 1996. However, ProstaScint® was only able to bind to the intracellular epitope of PSMA and was therefore not capable of

visualizing viable PC cells leading to poor clinical performance[25]. Since then, the class of PSMA targeting agents that have been most extensively explored are the urea-based small molecule inhibitors of PSMA. Two of these, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, have recently been approved by the FDA for PET imaging of PSMA positive lesions in men with PC with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum PSA level. The updated National Comprehensive Cancer Network Guidelines® for PC (Version 3.2022)[26] specify that ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL or PET/CT can be considered as an alternative to standard imaging of bone and soft tissue for initial staging, the detection of biochemically recurrent disease, and as workup for progression with bone scan plus CT or MRI for the evaluation of bone, pelvis, and abdomen. However, the performance of PSMA-targeting agents seems to be affected by serum PSA levels and risk factors such as Gleason score and tumor stage[27,28]. As the biochemically recurrent disease is characterized by heterogeneity, a PET agent targeting an alternative receptor such as GRPR may allow for better staging and hence more accurate treatment of biochemically recurrent PC. Indeed, clinical studies comparing GRPR-targeting PET to PSMA-targeting PET in the same patients highlighted the distinct distribution of the two targets in biochemically recurrent PC[14,17,29]. Immunohistochemistry analysis of radical prostatectomy specimens confirmed that the expression of PSMA and GRPR in PC tumors are not correlated[30].

The approved PSMA agents, as well as the GRPR agents under investigation, utilize radionuclides with a relatively short half-life, which requires PET to be conducted around 1 hour post administration. However, most PC lesions present with increased uptake and contrast at later imaging timepoints[31]. Thus, ^{64}Cu with its longer half-life ($t_{1/2}$=12.7 hours) compared to ^{68}Ga ($t_{1/2}$=68 minutes) and ^{18}F ($t_{1/2}$=109.7 minutes) has the potential to provide advantages over the ^{68}Ga- and ^{18}F-based PET products. Delayed imaging may enable the detection of additional or smaller lesions, due to enhanced tumor-to-background ratios following biological clearance of the product over time[32]. A longer half-life also allows for large-scale central manufacturing and offers logistical advantages in the manufacture and delivery of a finished product to the clinical site, providing superior geographical coverage compared to ^{68}Ga- and ^{18}F-based products. Thus, ^{64}Cu-SAR-BBN PET/CT has the potential to be a useful diagnostic tool to localize PC, including in patients with suspected biochemical recurrence of PC with a negative PSMA PET, where there is a high unmet medical need.

2.3 Preclinical Experience

A number of non-clinical studies have been conducted to assess the binding affinity, biodistribution, *in vivo* safety and tolerability, as well as tumor imaging of SAR-BBN labeled with either unlabeled SAR-BBN or SAR-BBN labeled with natural stable Cu (^{nat}Cu), ^{64}Cu, or Copper-67 (^{67}Cu).

Preclinical imaging studies with ^{64}Cu-SAR-BBN in a PC xenograft model showed high uptake and retention of the product in the tumor over 24 hours (19.6% Injected Activity [IA]/g at 1 hour and 7.9 % IA/g at 24 hours post dose)[33].

A repeat-dose toxicology study in male and female mice was conducted to investigate the potential toxicity of SAR-BBN when administered weekly for four administrations by intravenous (IV) injection. The study was performed using a 1:1 mixture of ^{nat}Cu labeled SAR-BBN and unlabeled SAR-BBN (Cu-SAR-BBN). Abnormal clinical signs were observed on injection days in treated mice only. Fully reversible microscopic findings were observed in male mice treated with 2 mg/kg Cu-SAR-BBN. These findings were not considered to be adverse. [redacted]

^{64}Cu-SAR-BBN and ^{67}Cu-SAR-BBN form a true theranostic pair, meaning the products behave the same biologically, as they both utilize isotopes of copper, for diagnosis and therapy, respectively. Biodistribution studies using either ^{64}Cu-SAR-BBN or ^{67}Cu-SAR-BBN are therefore applicable to both products. The biodistribution of ^{67}Cu-SAR-BBN was investigated in healthy male and female mice. ^{67}Cu-SAR-BBN was utilized to allow measurements of the biological clearance of Cu-SAR-BBN out to nine days after injection, due to the longer half-life of ^{67}Cu ($t_{1/2}$= 2.6 days). Effective blood clearance of ^{67}Cu-SAR-BBN was demonstrated in male and female mice at 1 hour (0.8 ± 0.2% IA/g and 1.1 ± 0.2% IA/g). At 24 hours, activity circulation in the blood had reduced by over 54 and 70% of the 1 hour values. The expression of GRPR in the pancreas resulted in high initial pancreas uptake, with the highest accumulated activity at 1 hour in both male and female mice (19.4 ± 10% IA/g and 22.3 ± 10.5% IA/g). However, over 75% and 97% of the ^{67}Cu-SAR-BBN activity in the pancreas had been cleared at 4 and 24 hours by the mice, respectively. Most peptides are subject to renal re-absorption and retention in the kidneys. ^{67}Cu-SAR-BBN showed low uptake in the kidneys, even at 1 hour (3.8 ± 0.5% IA/g and 6.2 ± 0.7 IA/g for males and females, respectively), and further reduction in time, suggesting a fast renal clearance. Uptake in the liver and intestines suggests there is also hepatobiliary clearance of ^{67}Cu-SAR-BBN.

Dosimetry calculations from a mouse biodistribution study enabled organ radiation dose extrapolations for an adult human male. [redacted] The effective whole-body dose for an adult male was estimated as 0.018 mSv/MBq [redacted]

Please refer to the current IB for further details on non-clinical studies.

2.4 Clinical Experience

One Investigator-led first-in-human clinical trial using ^{64}Cu-SAR-BBN has been conducted in Australia:

- **The C-BOBCAT trial:** *Pilot trial assessment of the diagnostic value of Cu64 SAR-Bombesin PET/CT imaging for staging of estrogen receptor/progesterone receptor positive human epidermal growth factor receptor 2 negative breast cancer patients with metastatic disease in comparison with conventional imaging (CT, bone scan and ^{18}F-FDG PET/CT)* (ACTRN12619001383156). Recruitment is completed in this study. Seven participants received a single administration of 200 MBq of ^{64}Cu-SAR-BBN. The aim of the study was to investigate the diagnostic accuracy of ^{64}Cu-SAR-BBN compared to conventional staging/restaging imaging, as well as to perform radiation dosimetry of ^{64}Cu-SAR-BBN.

Based on the data accrued to date, no significant safety findings have emerged in relation to ^{64}Cu-SAR-BBN. Dosimetry results are presented in Section 2.5.2.

2.5 Rationale for the Study and Study Design

The non-clinical and clinical data indicate the ^{64}Cu-SAR-BBN binds to GRPR-expressing tumors with high affinity, appears to be well-tolerated and has a potential to be used to obtain high quality images of GRPR-expressing tumors in human cancers. These findings warrant further investigations in clinical studies.

This is a multi-center, single arm, non-randomized, open-label study of ^{64}Cu-SAR-BBN administered to participants with biochemical recurrence of PC following definitive therapy.

The aim of the study is to evaluate the safety, pharmacokinetics, and efficacy of ^{64}Cu-SAR-BBN. The collection of standard safety parameters used in this study such as adverse event (AE) reporting, vital signs, electrocardiograms (ECGs), and clinical laboratory assessments are considered appropriate for monitoring the health and well-being of participants in early phase clinical studies. The biodistribution assessments were selected to characterize the pharmacokinetics of ^{64}Cu-SAR-BBN in humans. The assessments performed in this study to evaluate diagnostic efficacy are widely used and considered appropriate for the evaluation of performance of diagnostic imaging agents.

This study will provide the Sponsor with information on the safety, pharmacokinetics and diagnostic performance of ^{64}Cu-SAR-BBN in the target population, prior to initiating more extensive Phase 3 studies.

2.5.1 Imaging Timepoint Selection

The ^{64}Cu diagnostic radionuclide has a t½ of 12.7 hours which allows for the completion of PET scans up to at least 24 hours post administration of the radiopharmaceutical.

Preclinical studies with PET/CT images captured at 1, 4 and 24 hours post administration of ^{64}Cu-SAR-BBN showed that the tumor is clearly visible at the 1 hour timepoint. The tumor-to-background ratio at 4 and 24 hours was much higher than at 1 hour, demonstrating a high degree of accumulation and retention[33].

For this study, a PET/CT scan completed between 1 and 4 hours post dose of ^{64}Cu-SAR-BBN (Day 0 scan) is considered to be clinically practical and suitable to assess whether ^{64}Cu-SAR-BBN is capable of detecting PC in humans. Imaging at 24 hours post dose (Day 1 scan) will also be completed as it is hypothesized that delayed imaging may enable the detection of smaller lesions due to enhanced tumor-to-background ratios following biological clearance of the product over time.

2.5.2 Dose Selection of ^{64}Cu-SAR-BBN

^{64}Cu-SAR-BBN will be administered at a fixed administered activity of 200 MBq.

^{64}Cu-SAR-BBN dosimetry has been calculated from the Investigator-led study in female patients with breast cancer and demonstrated that a diagnostic administered activity (200 MBq) of ^{64}Cu-SAR-BBN can be used safely with only a low radiation burden to the patient. Overall, the whole-body effective dose was estimated to be 0.0095 mSv/MBq or 1.9 mSv for a 200 MBq injection of ^{64}Cu-SAR-BBN. An effective dose of this magnitude is comparable and below the risks associated with other routinely used imaging agents such as ^{18}F-FDG (8.4 mSv according to the Nuclear Medicine Radiation Dose Tool - SNMMI), and the recently approved ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL at their recommended administered activity (4.4 mSv and 3.9 mSv, respectively, according to approved labeling). The clinical biodistribution study projected that the pancreas was the organ with the highest absorbed dose, but with good clearance over 24 hours. A 200 MBq administered activity of ^{64}Cu-SAR-BBN will limit the estimated radiation absorbed dose to the pancreas to approximately 38.8 mGy, while the absorbed dose to the kidneys and bone marrow would be approximately 7.2 mGy and 2.6 mGy, respectively.

Based on the data obtained to date in the C-BOBCAT study, the Sponsor believes that 200 MBq of ^{64}Cu-SAR-BBN is an adequate activity to guarantee sufficient image quality for this study across the selected imaging timepoints.

2.6 Benefit/Risk Assessment

It is not known if study participants will gain any improvement in their own healthcare outcomes as a result of their participation in this study. However, the ability to accurately identify and stage PC recurrence would enable more effective treatment decisions and this would therefore, be considered a benefit to the participant. A general societal benefit is widely considered to accrue from medical scientific knowledge accumulated through the conduct of ethical research on participants.

All study participants will receive a single administration of ^{64}Cu-SAR-BBN. Specific foreseeable risks to study participants include:

- Radiation dose received by the study participant: A first-in-human study of ^{64}Cu-SAR-BBN in seven female participants with breast cancer estimated that an administration of 200 MBq of ^{64}Cu-SAR-BBN would result in an effective whole-body dose of 1.9 mSv, which is comparable to the whole-body effective doses of other routinely used imaging agents at their recommended administered activity. There is a potential hazard from the additional radiation burden to study participants. The study also involves low dose CT scan(s) performed for attenuation correction of the PET scan(s) and for the anatomical correlation to allow more precise delineation of organs.
- Chemical toxicity of ^{64}Cu-SAR-BBN and other constituents of the injection: The constituents (including excipients and stabilizers) of ^{64}Cu-SAR-BBN are at concentrations that are known to be safe for human use. ^{64}Cu-SAR-BBN, as supplied, will result in a maximum quantity not exceeding 100 µg of peptide mass per participant for an administration. The administered peptide mass is therefore at least 96 times less than the dose of Cu-SAR-BBN that has been demonstrated to be without any relevant toxicity in rodent toxicology studies (based on a 60 kg subject). The administered dose is well below the limits specified by the FDA for microdosing studies.
- Intravenous administration: Minor pain may occur at the time of venipuncture and minor bruising may also result; however, patients are exposed to these same risks during routine care. Whilst extravasation of PET radiopharmaceuticals is possible, it is unlikely associated with adverse outcomes due to the very small mass of materials contained in the injection, and the small amount of radioactivity available for injection. Nevertheless, an indwelling canula can be established prior to investigational product administration to mitigate this risk.
- Incidental findings of possible clinical significance: Appropriate diagnostic testing can assist in making a correct diagnosis and in providing additional information to guide patient management. An incorrect diagnosis (e.g., false negative or false positive results of the diagnostic tests) can have important consequences in patient management. An incidental finding is an imaging finding of potential health importance concerning the study participant, which is discovered while conducting imaging research, but is beyond the aims of the study. It is the responsibility of the local site or of the study Investigator to arrange for routine clinical review of study scans and clinical follow-up, as required. Policies for the communication of the incidental finding to the research participant should align with national regulations and customs. As part of the informed consent process, research participants will be informed about the possibility that incidental imaging findings may be detected, and about the pathway for handling such findings.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

The primary study objectives and endpoints to be evaluated in this study are presented in Table 1.

Table 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 AEs and 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 CDR, defined as the proportion of 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 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.

Abbreviations: AE = adverse event; CDR = correct detection rate; CT = computed tomography; PET = positron emission tomography; PC = prostate cancer; PPV = positive predictive value; SAE = serious adverse event; TP = true positive

3.2 Secondary Objectives and Endpoints

The secondary study objectives and endpoints to be evaluated in this study are presented in Table 2.

Table 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 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 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 FPR ^{64}Cu-SAR-BBN PET/CT.	• Participant-level 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 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 TNR of ^{64}Cu-SAR-BBN PET/CT.	• Participant-level 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.

Abbreviations: CT= computed tomography; DR= detection rate; FP= false positive; FPR= rate of false positive; PET= positron emission tomography; PPV= positive predictive value; SUV= standardized uptake value; TN= true negative; TNR= rate of true negative; TP= true positive

3.3 Exploratory Objectives and Endpoints

The exploratory study objectives and endpoints to be evaluated in this study are presented in Table 3.

Table 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, PPV and DR of ^{64}Cu-SAR-BBN 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-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.

Abbreviations: CDR= correct detection rate; CT= computed tomography; DR= detection rate; PC= prostate cancer; PET= positron emission tomography; PPV= positive predictive value; TP = true positive

4 STUDY DESIGN

4.1 Study Overview

Approximately 50 participants are planned to be enrolled in this study. This is a multi-center, single arm, non-randomized, open-label study of ^{64}Cu-SAR-BBN administered to participants with biochemical recurrence of PC following definitive therapy. To be considered for inclusion in the study, candidates must demonstrate negative or equivocal findings for PC on approved PSMA (^{68}Ga-PSMA-11 or ^{18}F-DCFPyL) PET and anatomical imaging (CT and/or MRI) and other conventional imaging, if available.

Participants who provide informed consent will undertake screening visit(s) to determine their eligibility to participate in the study. The maximum Screening period for each participant is 28 days. 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 maximum 180-day Follow-Up period to verify the ^{64}Cu-SAR-BBN PET/CT findings by:

- **Follow-up conventional imaging:** All participants will undergo conventional imaging at 90 days ± 15 days post Day 0.
    - Participants who are deemed to be negative or equivocal for PC recurrence based on central review of the 90-day conventional imaging will undergo further conventional imaging at 180 days ± 15 days post Day 0.
    - Participants who are deemed positive for PC recurrence based on central review of the 90-day conventional imaging will require no further study visits. However, if additional follow-up imaging per Investigator discretion is acquired within 180 days post Day 0, these data must be provided to the central reading center.
- **Histopathology:** 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) within 180 days of Day 0. 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**.
- **Assessment of PSA levels:** PSA will be assessed in all participants at 90 days ± 15 days and if the participant is returning to the study site for further follow-up imaging, at 180 days ± 15 days post Day 0. If radiation therapy or other salvage focal therapy (e.g., cryotherapy) is initiated during the study (as long as no concomitant androgen-deprivation therapy [ADT] is given), PSA levels must be monitored every 4 weeks from the initiation of the therapy. Prostate specific antigen response (defined as total PSA decline by ≥50% from baseline) must be confirmed by a second value within 4 weeks.

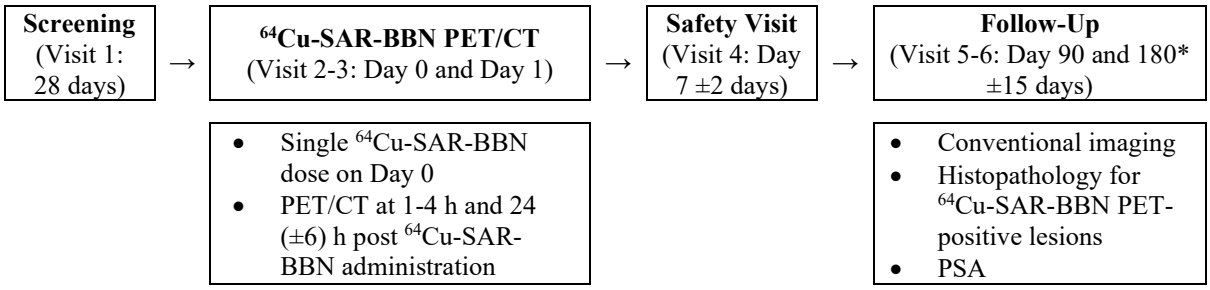
Central Review of Scans: The ^{64}Cu-SAR-BBN PET/CT scans will be interpreted by an appropriately qualified local Investigator and three independent, blinded, central readers. Each reader will be required to evaluate the PET/CT scans individually for the presence of pathological ^{64}Cu-SAR-BBN uptake in the prostate bed/gland, pelvic lymph nodes, extra pelvic lymph nodes, visceral/soft tissue and bone.

Expert Panel Composite Reference Standard: 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 Investigator will be required to submit all relevant clinical evidence available for the participant to enable the assessment of the Reference Standard. The expert panel will determine the composite Reference Standard without knowledge of the ^{64}Cu-SAR-BBN PET/CT results.

To assess the impact of ^{64}Cu-SAR-BBN PET/CT on disease management, the treating physician will be required to fill out a Pre-SAR-BBN and a Post-SAR-BBN Disease Management Form to provide information on the treatment strategy of the participant before and after the information from the local read of the ^{64}Cu-SAR-BBN PET/CT scan(s) becomes available.

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

4.2 Study Duration, Beginning and End of Study

Participants are considered enrolled in the study once they are appropriately consented and screened, with eligibility verified by an Investigator.

The total duration of the study is ~13 months.

The expected study recruitment period is ~6 months.

The maximum screening period for each participant is ~28 days.

The maximum on study period for each participant is ~6 months.

The end of study is defined as the date of the final participant visit/contact. In addition, Clarity may decide to terminate the study at any time (see Section 5.5).

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Study Population

The target study population is patients with biochemical recurrence of PC following definitive therapy and negative or equivocal findings for PC on approved PSMA PET and anatomical imaging (CT and/or MRI), and other conventional imaging, if available. The inclusion and exclusion criteria are outlined below.

5.1.1 Inclusion Criteria

Study candidates must meet all the following criteria to be eligible for the study:

1. At least 18 years of age.
2. Signed informed consent.
3. Life expectancy ≥ 12 weeks as determined by the Investigator.
4. Histologically confirmed adenocarcinoma of prostate per original diagnosis and completed subsequent definitive therapy.
5. Suspected recurrence of PC based on rising PSA after definitive therapy on the basis of:
    a. Post-radical prostatectomy: detectable or rising PSA that is ≥ 0.2 ng/mL with a confirmatory PSA ≥ 0.2 ng/mL (per American Urological Association recommendation); or
    b. Post-radiation therapy, cryotherapy, or brachytherapy: increase in PSA level that is elevated by ≥ 2 ng/mL above the nadir (per American Society for Therapeutic Radiology and Oncology-Phoenix consensus definition).
6. Negative or equivocal findings for PC on (1) approved PSMA PET and (2) anatomical imaging (CT and/or MRI), and (3) if available, any other conventional imaging performed as part of routine standard of care (SOC) imaging workup within 60 days prior to Day 0.
7. The Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
8. Adequate recovery from acute toxic effects of any prior therapy.
9. Estimated Glomerular Filtration Rate (eGFR) of 30 mL/min or higher.
10. Adequate liver function defined as alanine aminotransferase/aspartate aminotransferase <3 x upper limit of normal (ULN) and total bilirubin <1.5 x ULN (except in the case of Gilbert's syndrome).
11. For participants who have partners of childbearing potential: Partner and/or participant must use a method of birth control with adequate barrier protection.

5.1.2 Exclusion Criteria

Study candidates who meet any of the following criteria are not to be enrolled in the study:

1. Participants who received other investigational agents within 28 days prior to Day 0.
2. Participants administered any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives prior to Day 0.

3. Ongoing treatment or treatment within 90 days of Day 0 with any systemic therapy (e.g., ADT, antiandrogen, gonadotropin-releasing hormone, luteinizing hormone-releasing hormone agonist or antagonist) for PC.
4. Participants who are known to require prohibited treatment (e.g., initiation of ADT due to rapidly rising PSA) before the ^{64}Cu-SAR-BBN PET/CT results can be verified via histopathology or follow-up imaging.
5. Known or expected hypersensitivity to ^{64}Cu-SAR-BBN or any of its components.
6. Any serious medical condition or extenuating circumstance which the Investigator feels may interfere with the procedures or evaluations of the study.

5.2 Enrollment and Method of Assigning Participants to Treatment Groups

This is a non-randomized, single-arm study. After completing the screening period, participants who meet all eligibility criteria, will be enrolled into the study and receive a single administration of ^{64}Cu-SAR-BBN.

Each participant will be identified in the study by a Participant Number that is assigned when the participant is first entered into screening and is retained as the primary identifier for the participant throughout his entire participation in the trial. The Participant Number consists of the Center Number (as assigned by Clarity to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant Number available to the Investigator.

5.3 Study Blinding

This is a single-arm, 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.

5.4 Participant Withdrawal and Replacement

5.4.1 Screening Failures and Rescreening

5.4.1.1 Screen Failures

Screen failures are those participants who do not meet the study eligibility criteria. For participants who are considered a screen failure, the reason for screen failure will be entered on the Screening Log. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure participants. If the

participant experiences a serious adverse event (SAE) during the screening period, this information must also be entered (see Section 10.3 for SAE reporting details).

5.4.1.2 Rescreening

Participants who fail screening assessments may be re-screened. Rescreening and specific assessments to be repeated is to be discussed on a case-by-case basis with the Medical Monitor.

Rescreened participants should be assigned the same participant number as for the initial screening, which is deemed appropriate and practical from a reporting perspective. Participants may only participate in the study once.

5.4.2 Withdrawal of Consent and Discontinuation of Participants from the Study

Participants will be informed that they have the right to withdraw consent or discontinue from the study at any time for any reason, without prejudice to their medical care.

Following enrolment into the study, if a participant is discontinued or withdraws consent for any reason, whether related to the investigational product or not, the participant will be considered an early-discontinued participant. The reason for study discontinuation or withdrawal of consent is to be documented in the participants' source documents and electronic case report form (eCRF).

Refer to Section 5.4.2.1 for individual stopping rules.

1. Withdraw of Consent to Participate in the Study

Withdrawal of consent occurs only when a participant (or their substitute decision maker/person responsible) does not want to participate in the study any longer, does not want any further study related visits or assessments and does not want any further study related contact. The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation up until the point of withdrawal of consent. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a participant withdraws consent, the Investigator should make an effort to determine the primary reason for this decision (however the participant is not required to provide a reason) and record this information along with the withdrawal of consent discussion, which should be documented in the patient notes. With the participants consent, the Investigator may perform some final safety evaluations to ensure that there are no safety risks associated with the participants withdrawal. Further attempts to contact the participant for study related discussions are not allowed unless safety findings require communication or follow-up.

2. Investigator Decision to Discontinue the Participant

The Investigator also has the right to discontinue participants from the study for any of the following reasons:

- Participant non-adherence to protocol requirements;
- Any other reason based upon the medical judgment of the Investigator.

The Investigator will make every effort to ensure that early-discontinued participants who have received investigational product complete safety follow-up assessments (refer to Schedule of Assessments).

3. Lost to follow-up

Reasonable efforts will be made to keep in contact with enrolled study participants. Participants who have not responded to at least 3 such attempts for follow-up may be deemed 'lost to follow-up'. Efforts made to contact study participants must be documented in the participant's file.

5.4.2.1 Individual Stopping Rules

No individual stopping rules apply as only a single ^{64}Cu-SAR-BBN administration is delivered in the study.

5.4.3 Pregnancy

There is no information about the effects that ^{64}Cu-SAR-BBN could have on the development of the fetus in humans. Therefore, it is important that female partners of sexually active participants, do not become pregnant during the study and agree to use adequate contraception. Participants will be instructed that known or suspected pregnancy occurring during the study in female partners, should be confirmed and reported to the Investigator.

The Investigator should also be notified of a pregnancy of a female partner of the participant occurring during the study. In the event that a female partner of a participant is found to be pregnant whilst the participant is enrolled in the study, the pregnancy will be followed, and the status of mother and child will be reported to the Sponsor (or delegate).

A Pregnancy Report Form will be completed and submitted for any pregnancy occurring in female partners of male participants from enrollment until study completion.

5.4.3.1 Acceptable Forms of Contraception

Sexually active participants with female partners of childbearing potential are eligible to participate if they agree to follow 1 of the following methods of contraception consistently, starting from Screening, and for at least 5 days after the administration of ^{64}Cu-SAR-BBN:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent;
- Are sterilized (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate);
- Agree to use a male condom and have their partner use a contraceptive method with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant, and who agrees to the use of a condom by her partner.

Sexually active male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse; or use a male condom during each episode of penile penetration from Screening, and for at least 5 days after the administration of ^{64}Cu-SAR-BBN.

A highly effective method of contraception/birth control method which result in low failure rate (i.e., less than 1% per year when used consistently and correctly) must be used starting from the screening visit and for at least 5 days after the administration of ^{64}Cu-SAR-BBN.

Examples of acceptable contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception;
- Placement of an intrauterine device or intrauterine system;

Examples of non-acceptable methods of contraception include:

- Condoms alone or double barrier;
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation);
- Withdrawal;
- Spermicide.

5.4.3.2 Sperm Donation

Participants must refrain from donating sperm starting from Screening, during the study and for at least 5 days after the administration of ^{64}Cu-SAR-BBN.

5.4.4 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.

5.5 Premature Termination or Suspension of Study

The study can be temporarily suspended or prematurely terminated at any time for any reason by Clarity if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, and regulatory authorities.

Should this be necessary, the participants should be seen as soon as possible to perform the Safety Visit. Participants in long-term follow-up should also be contacted for a final visit. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests.

If the study is prematurely terminated or suspended, the Investigator will be responsible for promptly informing the institutional review board (IRB) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
- Demonstration of efficacy that would warrant stopping;
- Insufficient compliance to protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Sponsor terminates the study for administrative, financial or other reasons.

5.6 Safety Review Committee

A Safety Review Committee is not deemed necessary for this study based on what is known regarding the safety of ^{64}Cu from other studies. The medical monitor will periodically review laboratory and AE data and will review SAE reports in real time. Any clinically important findings will be discussed with the Investigators.

6 INVESTIGATIONAL PRODUCT

6.1 Dosage and Formulation

The investigational product administered in this study is ^{64}Cu-SAR-BBN. Clarity is developing this radiopharmaceutical for the diagnosis and management of 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 administered as a bolus IV injection. ^{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 FDA, and as such will be under controlled conditions for use in clinical trials.

Table 4 Investigational Product Administered

Investigational Product	Route of administration	Dose (MBq)	Dose Frequency
^{64}Cu-SAR-BBN	Intravenous Bolus Injection	200 MBq per administration	Single administration on Day 0

6.2 Supply, Packaging and Labeling

^{64}Cu-SAR-BBN will be manufactured, packaged, and labeled on behalf of Clarity and will be provided with appropriate documentation for human use.

^{64}Cu-SAR-BBN will be supplied as ready-to-use product according to production and quality control methods.

The release of each final batch of ^{64}Cu-SAR-BBN for human use is subject to the quality control measures (product specifications) established by Clarity, with quality control testing undertaken by the manufacturing facilities. Available analytical and production data for each batch will be reviewed by qualified personnel at the facility to ensure suitability for human administration.

6.3 Storage and Stability

^{64}Cu-SAR-BBN will be stored in a secure location (i.e., limited access area).

The Investigator (or suitably qualified designee) agrees not to dispense the ^{64}Cu-SAR-BBN from, nor store them at, any site other than the approved study sites as per local regulations.

Once prepared, ^{64}Cu-SAR-BBN is stored at room temperature in a butyl septum sealed, sterile, pyrogen-free glass vial with an expiration date and time designation on the label.

Refer to the IB for stability information.

^{64}Cu decays to stable (non-radioactive) daughter products.

6.4 Dispensing and Administration

^{64}Cu-SAR-BBN should be received, used, and administered only by suitably qualified persons at the study center. The receipt, storage, use, transfer, and disposal of ^{64}Cu-SAR-BBN is subject to the regulations and/or appropriate license of the study center.

^{64}Cu-SAR-BBN should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

^{64}Cu-SAR-BBN will be administered as a bolus IV injection under the supervision of the study Investigator or medically qualified delegate at a dosage of 200 MBq per administration of ^{64}Cu-SAR-BBN.

The Investigator or medically qualified delegate should ensure that the injected radioactivity is within ± 10% of prescribed activity.

6.4.1 Radiation Protection

^{64}Cu-SAR-BBN is a radiopharmaceutical, therefore it should only be used by personnel who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Radiation protection precautions must be taken in accordance with national and local regulations. Full details of restrictions and guidelines to the participant, friends, family and caregivers may be described in the informed consent form (ICF) and the IB.

6.5 Compliance and Accountability

The Investigator (or designee) is responsible for investigational product accountability, reconciliation, and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the Investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The amount of investigational products received from the Sponsor, and the amount administered to participants, and any amount accidentally or deliberately destroyed will be documented.

6.5.1 Storage of Supplies

Study materials will be stored by the study personnel according to the documentation provided with the study materials. The Sponsor reserves the right to inspect the investigational product storage area before and during the study.

6.5.2 Control of Supplies

Dispensing of the investigational products will be carefully recorded on appropriate investigational product accountability forms and will be verified by the study monitor during monitoring visits.

The accountability logs should include dates, quantities, batch numbers, and any unique pack numbers assigned to the investigational product and/or participant. The accountability logs will also include general details related to the study including the protocol, Sponsor and the Investigator.

6.5.3 Destruction of Supplies

The study monitor will review the investigational product accountability logs which detail the destruction of used and unused investigational products by the site.

6.6 Investigational Product Administration

6.6.1 Participant Preparation Prior to Dosing

There is no need for the participants to fast before the administration of ^{64}Cu-SAR-BBN.

6.6.2 Selection of Dose of ^{64}Cu-SAR-BBN

All participants will receive a single IV administration of 200 MBq of ^{64}Cu-SAR-BBN.

6.7 Participant Release and Radioprotection Precautions

Release of participants following administration of ^{64}Cu-SAR-BBN will be in accordance with any applicable regulations at the study center.

7 CONCOMITANT MEDICATIONS

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant receives during the study (refer to Schedule of Assessments) must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

If the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), the treatment and administration details must be recorded in the source documents and the eCRF.

The Medical Monitor must be notified of all prohibited medications administered to any participant, in order to assess the participant's eligibility to continue in the study.

Participants who are known to require prohibited treatment (e.g., initiation of ADT due to rapidly rising PSA) before the ^{64}Cu-SAR-BBN PET/CT results can be verified via histopathology or follow-up imaging should not be considered for participation in this study.

7.1 Required Treatments

Nil.

7.2 Permitted Treatments

All SOC treatments are permitted throughout the duration of a participant's involvement in the study with the exception of those treatments outlined in Section 7.3.

7.3 Prohibited Treatments

Treatment with investigational agents (that are likely to affect PSA levels or antineoplastic agents), saw palmetto, estrogens, steroids, testosterone supplements, 5ARIs (finasteride/dutasteride), and any antineoplastic therapy (with the exception of radiation or other salvage focal therapy with no concomitant ADT initiated following completion of Visit 4) is prohibited throughout the duration of the participant's involvement in the study.

Histopathological confirmation of PC prior to commencement of radiation or other salvage focal therapy is strongly encouraged.

Participants who receive prohibited treatment(s) should remain in the study until completion of Visit 4 to enable the assessment of safety.

8 STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments to be performed during the study. Unplanned visits not specified by the protocol or unscheduled assessments may be performed as clinically indicated at discretion of the Investigator; the associated data should be recorded on the relevant eCRF in support of an AE diagnosis or tumor assessments.

Refer to Table 5 for the Schedule of Assessments.

Table 5 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).

8.1 Demographics and Baseline Health Record

8.1.1 Baseline Demographics

Participant demographics will be recorded, including year of birth, gender, race, ethnicity.

Baseline disease characteristics will be recorded, including 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.

8.1.2 Medical and Medication History

Medical history will include evaluation for relevant past or present diseases or disorders, and relevant surgical history.

Medication history includes any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving within 14 days before signing informed consent must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

8.1.3 Prior Cancer Treatments and Therapies

As part of Screening assessments, review of prior PC treatments and therapies received from the time of diagnosis will be completed and recorded on the eCRF. This must include type and date of the initial definitive treatment modality (e.g., radical prostatectomy, radiation therapy, cryotherapy, or brachytherapy) and any ADT received.

8.2 Safety Assessments

8.2.1 Physical Examination

Full physical examinations will be performed by a registered physician (or qualified delegate). The full physical examination will include examination of the following: general appearance, cardiovascular system, respiratory system, and nervous system if vertebral involvement.

Any findings made during the physical examination must be noted regardless of if they are part of the participant's medical history.

Clinically significant observations will be recorded as AEs.

Note: Additional symptom directed physical examinations may also be performed at any time through the study as clinically indicated.

8.2.2 Body Weight and Height

Body weight (in kg) (wearing light clothes, no shoes) and height (in cm) will be measured (rounded to one decimal place).

8.2.3 Eastern Cooperative Oncology Group Performance Status

The ECOG (Table 6) is used by the Investigator to determine the score (0 to 5) that best represents the participants' activity status.

Table 6 Eastern Cooperative Oncology Group Performance Status Scale

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

Abbreviations: ECOG=Eastern Cooperative Oncology Group

8.2.4 Vital Signs

Vital signs measurements will include body temperature, respiratory rate, heart rate and systolic and diastolic blood pressure. Wherever possible, vital signs will be recorded after the participant has rested comfortably in a seated position with feet on the floor or in a supine position for at least 3 minutes (the position must be the same for a particular participant pre and post dose) and using consistent methods between participants.

Clinically significant observations, as deemed by the Investigator, will be recorded as AEs.

8.2.5 12-lead Electrocardiogram

Duplicate 12-lead ECGs will be performed after the participant has rested comfortably in the supine position for at least 3 minutes.

The following parameters will be assessed: heart rate, PR, RR, QRS, QT, QTcB (Bazett formula), QTcF (Fridericia formula). The Investigator (or a qualified delegate at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

Clinically significant observations, as deemed by the Investigator, will be recorded as AEs.

8.2.6 Clinical Laboratory Safety Assessments

Safety clinical laboratory samples will be analyzed at by the site's local laboratory.

Blood samples will be collected for the following tests:

- 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.

- 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.

- eGFR: will be calculated from creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and reported as mL/min. To convert mL/min/1.73m^2 to mL/min, multiply by the individual's Body Surface Area (calculated using the Mosteller formula) and divide by 1.73.

- Coagulation: prothrombin time, activated partial thromboplastin time, D-dimer. *Note: Coagulation may be assessed at any other timepoint, than specified in the Schedule of assessments, in case of an abnormal result, and followed until resolution.*

- Biochemical markers: Serum testosterone.

Urine samples will be collected for the following tests:

- Urinalysis: to include determination of glucose, protein, nitrites and leukocytes (dipstick test).

In the event of an unexplained, clinically significant abnormal laboratory test result, the test should be repeated and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

During the study, all out of range (abnormal) laboratory values, except for PSA, must be evaluated and commented on by the Investigator (or a qualified delegated observer at the investigational site) for clinical significance using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Clinically significant observations will be recorded as AEs unless they are associated with a diagnosis that itself has been reported as an AE (e.g., raised white cells and fever associated with an infection – in this case the infection is the AE and the lab value and fever are signs and symptoms of the AE and should not be reported separately).

8.2.7 Total Prostate Specific Antigen

As part of Screening, baseline PSA will be assessed; additionally, PSA results and dates of 2 previous most recent measurements (prior measurements are needed to assess PSA velocity/doubling time), PSA at initial diagnosis and PSA after initial definitive treatment (nadir) must also be recorded on the eCRF.

Prostate-specific antigen will further be assessed during the Follow-Up as specified in the Schedule of assessments. However, if radiation therapy or other salvage focal therapy (e.g., cryotherapy) is initiated during the study (as long as no concomitant ADT is given), PSA levels must be monitored every 4 weeks from the initiation of the therapy. Prostate-specific antigen response (defined as total PSA decline by ≥50% from baseline) must be confirmed by a second value within 4 weeks.

8.3 Imaging Assessments

8.3.1 Baseline Conventional Scans

Conventional imaging including an approved PSMA PET (such as ^{18}F-DCFPyL or ^{68}Ga-PSMA-11) and a CT and/or MRI must be performed within 60 days of Day 0. A diagnostic quality CT completed as part of a PET/CT scan is acceptable to serve as baseline anatomical imaging.

Any other available conventional scan(s) that is acquired within 60 days of Day 0 must also be reviewed as part of Screening to confirm study eligibility (e.g., whole-body ^{99m}Tc-MDP, ^{18}F-NaF, ^{18}F-fluciclovine, ^{11}C-choline scan, etc).

For each imaging modality, the date of acquisition and result (as positive, negative or equivocal for recurrent PC) must be reported on the eCRF. If equivocal, the site(s) of equivocal disease is also to be reported. All conventional scans will be assessed as per the site's local standard procedures.

All available scans completed within 60 days of Day 0 will be transferred in Digital Imaging and Communications in Medicine (DICOM) format to the central reading center with anonymization of participant specific information as specified in the Image Acquisition Manual.

8.3.2 ^{64}Cu-SAR-BBN PET/CT

The site will conduct the quantitative PET/CT according to the Image Acquisition Manual, which contains details of scan acquisition, processing parameters and quality assurance procedures. For a given participant, the same scanner must be used for all scan acquisition timepoints.

Participants will be asked to void prior to imaging. After voiding, a whole-body low dose CT and PET scan will be acquired starting from the mid-thigh to the skull vertex.

The PET/CT images will be transferred in DICOM format to the central reading center with anonymization of participant specific information as specified in the Image Acquisition Manual.

8.3.2.1 ^{64}Cu-SAR-BBN PET/CT Local Interpretation

The ^{64}Cu-SAR-BBN PET/CT scans will be interpreted locally by an appropriately qualified Investigator in a non-blinded fashion.

The reader will be required to evaluate the PET scans individually for the presence of pathological ^{64}Cu-SAR-BBN uptake in the prostate bed/gland, pelvic lymph nodes, extra pelvic lymph nodes, visceral/soft tissue and bone. Computed tomography scans from the PET/CT will be available to the readers to guide anatomical localization.

A ^{64}Cu-SAR-BBN PET-positive lesion will be defined as focal uptake that is greater than physiologic background uptake in that tissue[34] or greater than adjacent background if no physiologic uptake is expected and judged by the reader to be suspicious for disease. The number of PET-positive lesion(s) in each anatomical subregion will be documented.

Any incidental findings on the ^{64}Cu-SAR-BBN PET/CT scan(s) that are of potential clinical relevance and are not directly associated with the objectives of the protocol should be evaluated and handled by the Investigator as per standard medical/clinical judgment.

The processes for image acquisition, transmittal, and interpretation, including the list of regions and subregions to be assessed on the ^{64}Cu-SAR-BBN PET/CT are detailed in the Image Acquisition Manual.

8.3.2.2 ^{64}Cu-SAR-BBN PET/CT Central Interpretation

The central reading center will receive and evaluate the ^{64}Cu-SAR-BBN PET/CT scans. The scans will be interpreted by three different independent blinded readers in a random order at separate reading sessions. Central readers will be blinded as described in Section 5.3.

Computed tomography scans from the ^{64}Cu-SAR-BBN PET/CT will be available for anatomic correlation.

The readers will be required to evaluate the PET scans individually for the presence of pathological ^{64}Cu-SAR-BBN uptake in the prostate bed/gland, pelvic lymph nodes, extra pelvic lymph nodes, visceral/soft tissue and bone. The same ^{64}Cu-SAR-BBN PET-positive lesion definition will be applied as for the local interpretation. Lesions that do not meet the criteria for a positive lesion but are deemed suspicious for PC will be recorded as equivocal. The number of lesion(s) in each anatomical subregion will be documented. The size (two axial dimensions), location, standardized uptake value (SUV)mean and max, lesion-to-background ratio and reader confidence level will be recorded for up to 15 soft tissue lesions and 10 bone lesions by the central readers.

The processes for image acquisition, transmittal, and interpretation are detailed in the Image Acquisition Manual and Imaging Review Charter.

8.3.3 Follow-up Conventional Imaging

Follow-up conventional imaging must be acquired for all participants as specified in the Schedule of Assessments, regardless of the ^{64}Cu-SAR-BBN PET/CT findings.

The follow-up conventional imaging must include the same modality/modalities as the conventional imaging performed at baseline to allow for reproducible and accurate comparisons. This should include anatomical imaging (MRI or CT; a diagnostic quality CT completed as part of a PET/CT scan is acceptable), and the same approved PSMA PET as completed at baseline. Scan acquisition will be completed according to institutional protocols.

The imaging modality, date of acquisition and result (including number of lesions suspicious for PC within each anatomical subregion) must be recorded on the eCRF.

All scans will be transferred in DICOM format to the central reading center with anonymization of participant specific information as specified in the Image Acquisition Manual.

Note: Additional follow-up conventional imaging may be completed at any other timepoint, outside of those specified in the Schedule of assessments, 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.

8.4 Histopathology

Where clinically feasible, histopathology (from image-guided biopsy or surgery [e.g., salvage pelvic lymph node dissection]) should be obtained 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**. The biopsy or surgery specimens will be processed and analyzed locally.

The procedure, date of assessment, imaging modality used to guide biopsy (if applicable) and local histopathology result will be recorded on the eCRF.

For participants undergoing image-guided needle biopsy, the needle biopsy images (e.g., CT, transrectal ultrasound-MRI, ultrasound) of the procedure will be sent to central reading center. The instruction for capturing biopsy images and directions for submitting the images to the central reading center is specified in the Image Acquisition Manual.

All histopathology results (and any associated images) acquired within 180 days (±15 days) of Day 0 must be transferred to the central reading center.

8.5 Prostate Cancer Treatments

Any PC treatment that the participant receives during the study must be recorded on the eCRF.

This includes single agent or combination in order of administration, start and stop dates, dose(s), and schedule(s), the disease state in which it was administered (biochemical recurrence or M1; for M1 specify if node, visceral/soft tissue or bone), response (resistant or sensitive) on the basis of PSA if appropriate; and type of progression (PSA, radiographic [bone, nodal, visceral], clinical [e.g., pain escalation]) if applicable.

For radiation therapy, target region(s), dose (Gy) and number of fractions should be recorded.

8.6 Diagnostic Efficacy Assessments

8.6.1 Assessment of the Composite Reference Standard

The composite Reference Standard may consist of histopathology, conventional imaging modalities that are routinely used in the diagnosis and staging of PC and PSA levels. ^{64}Cu-SAR-BBN scans will not form part of the Reference Standard.

The Reference Standard status will be determined by an independent, blinded, central expert panel. The expert panel will establish the Reference Standard disease status (on a participant- and region-level) for each participant individually, using information provided by the site's Investigator. The experts will be blinded as described in Section 5.3.

The Investigator will be required to submit all relevant clinical evidence available for the participant to enable the assessment of the Reference Standard. Relevant evidence will include:

- All available histopathology reports related to the participants disease history;
- All available conventional scans and related local reports collected as part of Screening (within 60 days of Day 0) and Follow-up (within 180 days [±15 days] of Day 0);
- PSA levels recorded as part of Screening and Follow-up;
- All available PC related symptom and treatment history.

The composite Reference Standard will be hierarchical in nature, with three levels of evidence that will be applied as follows:

- **Level 1:** Evaluable histopathology from biopsy or surgery OR in case that histopathology is not available, inconclusive or negative:
- **Level 2:** Conventional imaging procedures OR if neither histopathology or conventional imaging are available or informative:
- **Level 3:** Confirmed PSA response following radiation or other salvage focal therapy (as long as no concomitant ADT is given), defined as total PSA decline by ≥50% from baseline, confirmed by a second value within four weeks as per the Prostate Cancer Working Group 3 criteria[35].

The expert panel will use the collective information to determine and record each region with histopathology demonstrating PC, the number of lesions suspicious for PC detected on

conventional imaging in each anatomical subregion and whether the participant achieved confirmed PSA response (if applicable).

Region(s) with no histopathology demonstrating PC or no unequivocal lesion recorded in any of the anatomical subregions on conventional imaging will be deemed negative for the region level Reference Standard status.

Region(s) with histopathology demonstrating PC will qualify the region as positive for the region level Reference Standard status. A subregion with at least one unequivocal lesion (or cluster of lesions or diffuse sclerotic metastasis) on conventional imaging will qualify the subregion as positive for the Reference Standard status.

If the expert panel judged that the available information is insufficient to provide a reliable conclusion, the result will be recorded as non-evaluable (e.g., no follow-up assessments were completed). The reason for selecting a non-evaluable or inconclusive result will be documented.

Further details on the process and interpretation of the conventional imaging will be provided in the Imaging Review Charter.

8.6.2 Assessment of Reference Standard against the ^{64}Cu-SAR-BBN PET/CT Results

For the assessment of the Reference Standard against the ^{64}Cu-SAR-BBN PET/CT, region-level matching will be used for histopathology, subregion-level matching for imaging, and participant-level matching for PSA response to radiation or other salvage focal therapy (refer to Section 8.6.1). Matching the Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results will be completed via statistical programming.

Assessment of **region-level** Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results:

- Histopathology: A region that is ^{64}Cu-SAR-BBN PET-positive (i.e., includes at least one unequivocal PET-positive lesion) and Reference Standard positive, will be assigned as true positive (TP) for the region-level status.
- 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), will be assigned as TP. A region that includes at least one TP subregion will be assigned as TP for the region-level status.
- A region that is ^{64}Cu-SAR-BBN PET-positive (i.e., includes at least one unequivocal PET-positive lesion) and is Reference Standard negative based on at least 1 evaluable timepoint, will be assigned as false positive (FP) for the region-level status.
- A region that is ^{64}Cu-SAR-BBN PET-negative (i.e., no unequivocal PET-positive lesion or only equivocal lesion(s) detected within the subregions) and Reference Standard negative, will be assigned as true negative (TN) for the region-level status.
- A region that has either a non-evaluable ^{64}Cu-SAR-BBN result for a specific timepoint or has a non-evaluable or inconclusive Reference Standard will not be assigned for that timepoint.

Assessment of **participant-level** Reference Standard against the ^{64}Cu-SAR-BBN PET/CT results:

- A participant with at least one TP region AND/OR at least one unequivocal ^{64}Cu-SAR-BBN PET-positive lesion and confirmed PSA response to radiation or other salvage focal therapy, will be assigned as TP for the participant-level status.
- A participant with at least one unequivocal ^{64}Cu-SAR-BBN PET-positive lesion who does not meet the above criteria to be deemed TP, will be assigned as FP for the participant-level status.
- A participant with a negative ^{64}Cu-SAR-BBN PET/CT (i.e., no unequivocal PET-positive lesion or only equivocal lesion(s) detected on the scan) and negative Reference Standard, will be assigned as TN for the participant-level status.
- A participant that has either a non-evaluable ^{64}Cu-SAR-BBN result for a specific timepoint or has a non-evaluable or inconclusive Reference Standard will not be assigned for that timepoint.

False negative results (on a region- or participant-level) will not be assigned in the study. A participant with negative baseline conventional imaging and negative ^{64}Cu-SAR-BBN PET/CT imaging, who later demonstrates a positive result at follow-up conventional imaging (e.g., during the 90-day follow-up imaging) will not be considered a false negative 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. A positive follow-up scan must therefore be interpreted with caution as it may reflect a different disease state compared to the one evaluated during the baseline conventional and ^{64}Cu-SAR-BBN PET/CT imaging period.

A positive ^{64}Cu-SAR-BBN PET/CT within the target study population may indicate that this new imaging agent is more sensitive in detecting early recurrence than other available modalities. The 90- and 180-day follow-up timelines have been selected to allow for further development of the disease so the positive ^{64}Cu-SAR-BBN PET/CT findings can be validated using conventional, potentially less sensitive reference modalities. The selected follow-up timelines therefore enable evaluation of the diagnostic efficacy endpoints that relate to positive findings, but do not allow for a reliable assessment of false negative results.

8.6.3 Disease Management Plan

The treating physician will be required to fill out a Pre-SAR-BBN and a Post-SAR-BBN Disease Management Form to provide information on the treatment strategy of the participant before and after the information from the local read of the ^{64}Cu-SAR-BBN PET/CT scan(s) becomes available.

The Pre-SAR-BBN Disease Management Form must be completed during Screening by the treating physician to document the initial intended management plan for the participant based on available clinical information and conventional imaging results.

The 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). This 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). Additionally, the operator will be asked to indicate which ^{64}Cu-SAR-BBN PET/CT timepoint has influenced the assessment. If both timepoints influenced the assessment (whether for change or not) both should be selected.

8.7 Pharmacokinetics

8.7.1 Biodistribution of ^{64}Cu-SAR-BBN

The biodistribution of ^{64}Cu-SAR-BBN utilizing the PET/CT scans will involve the calculation of:

- Maximum and mean SUVs in lesion(s), visceral/soft tissue, bone;
- Lesion-to-background ratio.

All biodistribution measures will be assessed centrally, according to the study Imaging Review Charter to ensure a high and consistent level of quantification across all sites.

9 VISIT-SPECIFIC PROCEDURES

9.1.1 Screening Period

9.1.1.1 Visit 1 (Day -28 to Day 0)

The following assessments must be performed/obtained within the 28 days before the participant receives the ^{64}Cu-SAR-BBN administration. 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.

Results of SOC tests or examinations performed prior to obtaining informed consent and within 28 days (within 60 days for the conventional scans) prior to the ^{64}Cu-SAR-BBN administration may be used; such tests do not need to be repeated for screening.

If the start date for the ^{64}Cu-SAR-BBN administration extends beyond 28 days from the start of the screening assessments (e.g., due to issues related to logistics), the Investigator in consultation with the Medical Monitor must determine if any screening assessments need to be repeated.

Assessments to be completed:

- Informed Consent (Refer to Section 12.512.5)
- Inclusion/Exclusion Criteria (Refer to Section 5.1)
- Demographic Data (Refer to Section 8.1.1)
- Medical and Medication History (Refer to Section 8.1.2)
- Prior Cancer Treatments (Refer to Section 8.1.3)
- Body Weight and Height (Refer to Section 8.2.2)
- ECOG Status (Refer to Section 8.2.3)
- Hematology (Refer to Section 8.2.6)
- Biochemistry (Refer to Section 8.2.6)
- Coagulation (Refer to Section 8.2.6)
- eGFR (CKD-EPI formula) (Refer to Section 8.2.6)
- Serum Testosterone (refer to Section 8.2.6)
- Total PSA (Refer to Section 8.2.7)
- Conventional Imaging (Refer to Section 8.3.1)
- Adverse Events (ongoing) (Refer to Section 10.1)
- Concomitant Medications (ongoing) (Refer to Section 7)
- Pre-SAR-BBN Disease Management Form (Refer to Section 8.6.3)

9.1.2 ^{64}Cu-SAR-BBN PET/CT Imaging

9.1.2.1 Visit 2 (Day 0)

Enrolled participants who meet all eligibility criteria will receive a single ^{64}Cu-SAR-BBN administration followed by a PET/CT scan. Pre-dose assessments will be completed prior to the administration of ^{64}Cu-SAR-BBN. Post-dose assessments will be completed as per the assessment windows specified below.

Assessments to be completed:

- Adverse Events (ongoing)
- Concomitant Medications (ongoing)

Pre dose

- Body Weight (Refer to Section 8.2.2)
- Physical Exam (Refer to Section 8.2.1)
- Vital Signs (Refer to Section 8.2.4)
- Duplicate 12-Lead ECG (Refer to Section 8.2.5)
- Urinalysis (dipstick) (Refer to Section 8.2.6)

^{64}Cu-SAR-BBN Dose (Refer to Section 6.4 for dosing and administration details)

Post dose

- Vital Signs to be completed prior to the ^{64}Cu-SAR-BBN PET/CT (Refer to Section 8.2.4)
- Duplicate 12-Lead ECG to be performed at 30 min (±10 min) post ^{64}Cu-SAR-BBN administration (Refer to Section 8.2.5)
- ^{64}Cu-SAR-BBN PET/CT to be performed at 1 to 4 hours post ^{64}Cu-SAR-BBN administration (Refer to Section 8.3.2)

9.1.2.2 Visit 3 (24 hours ±6 hours Post Dose, Day 1)

This visit is to take place approximately 24 hours after the ^{64}Cu-SAR-BBN administration.

Assessments to be completed:

- Adverse Events (ongoing)
- Concomitant Medications (ongoing)
- ^{64}Cu-SAR-BBN PET/CT (Refer to Section 8.3.2)

9.1.3 Safety Visit

9.1.3.1 Visit 4 (Day 7 ± 2 days)

This visit is to take place 7 days (± 2 days) after the ^{64}Cu-SAR-BBN administration.

Assessments to be completed:

- Adverse Events (ongoing)
- Concomitant Medications (ongoing)
- Record Any Prostate Cancer Treatments (Refer to Section 8.1.4)
- Physical Exam (Refer to Section 8.2.1)
- Body Weight (Refer to Section 8.2.2)
- Vital Signs (Refer to Section 8.2.4)
- Hematology (Refer to Section 8.2.6)
- Biochemistry (Refer to Section 8.2.6)
- Coagulation (Refer to Section 8.2.6)
- eGFR (CKD-EPI) (Refer to Section 8.2.6)
- Urinalysis (Refer to Section 8.2.6)
- Additional Imaging/Histopathology (Refer to Section 8.3.3 and 8.4)
- Post-SAR-BBN Disease Management Form (Refer to Section 8.6.3)

9.1.4 Follow-Up

9.1.4.1 Visit 5 (Day 90 ± 15 days)

This visit is to take place 90 days (± 15 days) after the ^{64}Cu-SAR-BBN administration. All participants must complete this visit, regardless of the ^{64}Cu-SAR-BBN PET/CT results.

Participants who based on the central expert panel's interpretation of the follow-up conventional imaging completed during Visit 5 are deemed:

- **negative or equivocal for PC recurrence** - must continue to Visit 6.
- **positive for PC recurrence** - no further study visits are required.

Assessments to be completed:

- Record Any Prostate Cancer Treatments (Refer to Section 8.1.4)
- Total PSA (Refer to Section 8.2.6)
- Follow-up Conventional Imaging (Refer to Section 8.3.3)
- Record Any Additional Imaging/Histopathology (Refer to Section 8.3.3 and 8.4)

9.1.4.2 Visit 6 (Day 180 ± 15 days)

This visit is to take place 180 days (± 15 days) after the ^{64}Cu-SAR-BBN administration.

Only participants who were deemed negative or equivocal for PC recurrence based on the follow-up conventional imaging (as per the central expert panel's interpretation) completed during Visit 5 must complete Visit 6.

If the participant is not returning to Visit 6, but additional imaging/histopathology was acquired within 180 days (± 15 days) of Day 0, the relevant details must be recorded on the eCRF and information submitted to the central reading center.

Assessments to be completed:

- Record Any Prostate Cancer Treatments (Refer to Section 8.1.4)
- Total PSA (Refer to Section 8.2.6)
- Follow-up Conventional Imaging (Refer to Section 8.3.3)
- Record Any Additional Imaging/Histopathology (Refer to Section 8.3.3 and 8.4)

10 ADVERSE EVENT MONITORING

10.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse Events should be recorded from the time of informed consent until the completion of the Safety Visit. Adverse Events recorded before the administration of ^{64}Cu-SAR-BBN will be classified as non-treatment emergent AEs. All AEs recorded after the investigational product administration will be classified as treatment emergent AEs (TEAEs). Non-related AEs will only be reported and followed up until the Safety Visit. All related AEs are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized. An assessment should be made at the last study-related visit for each patient. Certain long-term AEs cannot be followed until resolution within the settings of this protocol. In these cases, follow-up will be the responsibility of the treating physician. If during AE follow-up the case has progressed to the level of SAE, or if a new SAE is observed whose relationship to the study medication cannot be ruled out, the situation must be reported by the Investigator becoming aware of the information.

Participants should be instructed to report any AE that they experience to the Investigator.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure. Adverse events should be entered into the eCRF within 5 days of reporting.

Clinically significant abnormal laboratory or other examination (e.g., ECG) findings that are detected during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Any event that in the opinion of the Investigator is solely due to the underlying disease should not be reported as an AE.

10.1.1 Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility; i.e., the relationship cannot be ruled out.

10.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For ^{64}Cu-SAR-BBN, the reference safety information is included in the current IB. The reference safety information is reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

10.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE according to Common Terminology Criteria for Adverse Events (CTCAE) criteria and will also categorize each AE as to its potential relationship to investigational product using the categories of related or not related.

10.1.3.1 Assessment of Severity

Severity of AEs will be graded according to the following definitions:

The Investigator will make an assessment of severity (intensity) for each AE and SAE reported during the study using the National Cancer Institute (NCI) CTCAE V5.0 criteria. The assessments will be based on the Investigator's clinical judgment. The severity of each AE and SAE recorded in the eCRF should be assigned to 1 of the following:

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 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.

Abbreviations: ADL=Activities of Daily Living

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

10.1.3.2 Causality Assessment

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship to ^{64}Cu-SAR-BBN. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

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

Related:	An AE that follows a temporal sequence from administration of the investigational product, or for which possible involvement of the investigational product cannot be ruled out, although factors other than the drug, such as underlying diseases, concurrent medical conditions, concomitant drugs and concurrent treatments, are also possibly responsible.
Not related:	An AE that does not follow a temporal sequence from investigational product administration and/or that can reasonably be explained by other factors, such as underlying diseases, concurrent medical conditions, concomitant drugs and concurrent treatments.

10.2 Serious Adverse Event

Any AE, due solely to the underlying disease or disease progression, should not be reported as an SAE, unless the study treatment contributed to the AE.

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

- Death;
- Life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in the view of the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.)

- Requires hospitalization or prolongation of existing hospitalization;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- An important medical event;

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or

surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.3 Serious Adverse Event Reporting – Procedures for Investigators

10.3.1 Initial Reports

All SAEs occurring from the time of consent until the Safety Visit must be reported within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to investigational product occurring until end of the Safety Visit must be reported to the Sponsor.

To report an SAE, complete the SAE Report Form and email the completed SAE Report Form within 24 hours of awareness. An SAE Report Form will be supplied with the study binder.

In addition to reporting the SAE to Sponsor (or designee), the Investigator must also notify the IRB which approved the study according to their requirements. Copies of all correspondence relating to reporting of any SAEs should be maintained in the site's study files and will be checked routinely by the study monitor.

If the Sponsor and the Investigator consider that the SAE is investigational product related (i.e., an adverse reaction) and unexpected it will be reported to the appropriate regulatory authorities by the Sponsor (or designee) within the pre-defined timelines.

10.3.2 Follow-Up Reports

The Investigator must continue to follow the participant until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the participant dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (e.g., deidentified participant discharge summary, autopsy reports), if requested.

10.4 Pregnancy

Pregnancies occurring in a female partner of a participant after the first administration of the investigational product require immediate reporting. They must be reported within 24 hours after the Investigator has become aware of the pregnancy. A pregnancy report will be completed and sent within 24 hours of becoming aware of the pregnancy. The Investigator will collect follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant that must also be reported to the Sponsor or designee. Upon awareness of the outcome of the pregnancy, the Investigator must forward a follow-up Pregnancy Report with any relevant information.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event within 24 hours of being notified of the pregnancy report.

10.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA and the IRBs, and in

any case no later than 7 calendar days after knowledge by the Sponsor of such a case, and relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA and the IRBs as soon as possible but within a maximum of 15 calendar days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

11 STATISTICAL METHODS

11.1 General Considerations

A Statistical Analysis Plan (SAP) will be written after finalizing the protocol and prior to database lock. The SAP will detail the implementation of all the planned statistical analysis in accordance with the principal features stated in the protocol. Any deviations from the SAP will be presented in the final clinical study report.

Continuous variables will be summarized by the number of subjects, mean, standard deviation, standard error of the mean, median, 25th quartile, 75th quartile, minimum, and maximum values.

Categorical variables will be summarized using frequency counts and percentages.

11.2 Analysis Populations

11.2.1 Enrolled Analysis Set

The Enrolled Analysis Set will include all participants who signed the ICF and were enrolled into the study. This analysis set will be used for patient disposition summaries.

11.2.2 Safety Analysis Set

The Safety Analysis Set will be used to assess all safety data and will include all participants who receive any amount of ^{64}Cu-SAR-BBN.

11.2.3 Full Analysis Set

The Full Analysis Set (FAS) will include all participants who receive any amount of ^{64}Cu-SAR-BBN and have ^{64}Cu-SAR-BBN PET/CT imaging results from at least one central reader. The FAS will be used for all efficacy analyses.

11.2.4 Biodistribution Population

The Biodistribution Analysis Set will include all participants in the Safety Analysis Set and have at least one biodistribution measure.

11.3 Determination of Sample Size

The co-primary endpoints include participant-level correct detection rate (CDR) or true positive detection rate and region-level positive predictive value (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%.

11.4 Analysis Methods

11.4.1 Enrollment and Disposition

Disposition of participants enrolled, treated, and completed the study will be summarized with reasons for study discontinuation for the Enrolled Analysis Set. The number and percentage of participants in each analysis set will also be presented.

11.4.2 Demographic and Other Baseline Characteristics

Baseline characteristics will be summarized for the Safety Analysis Set and the FAS. Demographic and baseline data including age, sex, race, ethnicity, ECOG status, weight, height and body mass index at baseline will be listed and summarized. Baseline PC characteristics, including but not limited to PC pathology results, PC staging, initial Gleason score, time from initial diagnosis, time from last biochemical recurrence, relevant symptom history, PSA level at baseline, and prior cancer treatment for PC will be summarized.

11.4.3 Prior and Concomitant Medication

Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug dictionary and tabulated by the Anatomical Therapeutic Chemical class and preferred term for the Safety Analysis Set. Any PC treatment during the study will also be summarized in the same manner.

Prior medications are defined as those medications which stopped prior to the administration of the investigational product. Concomitant medication are medications that are taken at least once after the start of the administration of the investigational product.

Prostate cancer treatment received during the study will also be summarized.

11.4.4 Safety Analysis

Safety parameters will include AEs, SAEs, laboratory assessments, vital signs, and ECG analysis. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

All safety analyses will be conducted in the Safety Analysis Set.

11.4.4.1 Adverse Event Analysis

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is any AE that occurs after the administration of the investigational product.

TEAEs, TEAEs related to investigational product, TEAEs with grade 3 or higher, TEAEs with grade 3 or higher related to investigational product, and treatment-emergent SAEs will be tabulated by MedDRA system organ class and preferred term.

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

11.4.4.2 Laboratory Data Analysis

Safety laboratory parameters and corresponding changes from baseline will be presented as descriptive statistics by visit. Shift tables based on the NCI-CTCAE v5.0 toxicity grading will be presented for selected laboratory parameter between baseline and the highest/lowest post-baseline NCI-CTCAE v5.0 toxicity grade. Any clinically significant abnormalities in laboratory values will be listed.

11.4.4.3 Vital Sign Analysis

Vital signs at each scheduled time point and changes from baseline will be summarized using descriptive statistics.

11.4.4.4 Electrocardiogram Analysis

For ECGs, all standard parameters (heart rate, RR, PR, QRS, QT, QTcF, and QTcB as applicable) at each scheduled time point along with changes from baseline will be summarized using descriptive statistics. The incidence of notable ECG changes in maximum absolute QTcF and QTcB intervals (> 450, > 480, and > 500 ms) over all post-treatment evaluations, as well as in QTcF and QTcB maximum changes from baseline (> 30 and > 60 ms) over all post-dose evaluations will be summarized.

A listing of ECG data will be provided.

11.4.5 Efficacy Analysis

Efficacy endpoints will be assessed using the FAS.

11.4.5.1 Primary Efficacy Analyses

The co-primary efficacy endpoints include the following:

- Participant-level CDR on Day 0 scan;
- Participant-level CDR on Day 1 scan;
- Region-level PPV on Day 0 scan;
- Region-level PPV on Day 1 scan.

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 follow-up reference standard datapoint (as without any follow-up reference data it is not possible to determine if the participant is TP or not, which may bias the results) and will be calculated as follows: CDR = TP/(all scanned participants with at least 1 evaluable reference datapoint).

Participants without a ^{64}Cu-SAR-BBN PET/CT scan at a 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 on a region-level for each central reader 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 follows: PPV = TP/(TP+FP).

Regions that are not positive on the ^{64}Cu-SAR-BBN PET/CT scan at a specific timepoint (Day 0 or Day 1) will be excluded for the region-level PPV calculation for that timepoint.

The anatomic regions for lesions include the following:

Region	Description of Anatomic Region
1	Prostatic
2	Pelvic lymph nodes
3	Extra pelvic lymph nodes
4	Visceral/soft tissue
5	Bone

The point estimates of CDR and PPV on Day 0 and on Day 1 will be computed along with the 2-sided 95% exact binomial CIs using the Clopper-Pearson method. The primary efficacy analyses will be performed for each central reader.

The following sensitivity analyses of the participant-level CDR and region-level PPV will be performed:

- Based on all participants in the FAS regardless of whether there are reference datapoints collected. Missing data will be handled as follows:
  - Worst-case imputation:
    - For the participant-level CDR on Day 0 and on Day 1 based on FAS, participants with missing/non-evaluable composite Reference Standard data will be imputed as non-true positive and included in the denominator.
    - For the region-level PPV calculation on Day 0 and on Day 1 based on FAS, PET/CT positive regions with missing/non-evaluable corresponding composite Reference Standard data will be imputed as FP and included in the denominator.
  - Tipping Point Analysis:
    - In addition, to examine the impact of missing or non-evaluable composite Reference Standard data and evaluate the robustness of the results, a tipping point analysis will be performed as a sensitivity analysis for participant-level CDR and region-level PPV based on the FAS, where participants with missing or non-evaluable composite Reference Standard data will be imputed as TP with probability of p ranging from 0 to 1 with an increment of 0.1 (p = 0 corresponds to none of the participants without Reference Standard information in a PET positive region will be imputed as true positive while p = 1 means all participants without Reference Standard information in a PET positive regions will be imputed as TP).

Details of handling of missing data will be fully described in the SAP.

11.4.5.2 Secondary Efficacy Analyses

Secondary efficacy endpoints include the following:

- Participant-level PPV on Day 0 and on Day 1;
- Participant-level DR on Day 0 and on Day 1;
- Participant-level FPR on Day 0 and on Day 1;

- Region-level FPR on Day 0 and on Day 1;
- Participant-level discrepant PET negative rate between Day 0 and Day 1;
- Participant-level TNR on Day 0 and on Day 1;
- Region-level TNR on Day 0 and on Day 1.

Secondary efficacy endpoints will be analyzed on the FAS. Point estimates and 2-sided 95% exact binomial CIs will be presented for each central reviewer separately.

11.4.5.3 Exploratory Efficacy Analyses

The exploratory efficacy endpoints include the following:

- Proportion of participants with any change in intended PC treatment due to either the Day 0 or Day 1 scan;
- Composite CDR, PPV and DR of the Day 0 and Day 1 scan;
- CDR, participant- and region-level PPV and DR of the Day 0 and/or Day 1 scan as a function of baseline variables;
- 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;
- Difference in the number of lesions detected per participant on the Day 0 versus the Day 1 scan;
- Lesion-level overall agreement rate on the Day 0 and Day 1 scans, on the Day 0 and reference scans, and on the Day 1 and reference scans;
- PSA over time and change from baseline;
- PSA velocity and PSA doubling time (PSADT) at the end of the study and at baseline.

Binary exploratory endpoints will be summarized with points estimates and corresponding 2-sided 95% exact binomial CIs based on the FAS.

Difference in the number of lesions detected per participant on the Day 0 versus the Day 1 scan will be summarized descriptively and compared using a paired *t*-test. Other exploratory endpoints including PSA value at each scheduled time point and change from baseline, PSA velocity, and PSADT will be summarized using descriptive statistics.

Descriptive statistics, graphical methods, and statistical modeling as appropriate may be used to explore the relationship between PET-positivity (biodistribution measures such as SUVs and lesion-to-background ratio) and true/false positivity.

In addition, CDR, PPV and DR may also be assessed as a function of the following baseline variables:

- PSA at baseline prior to the scan (<0.5, 0.5 - <1.0, 1.0 - <2.0, 2.0 - <5.0, ≥5);
- PSADT;
- PSA velocity;
- Testosterone at baseline;
- SUV mean and max;

- Lesion-to-background ratio;
- Initial treatment received;
- Any previous ADT administered;
- PSMA PET at baseline (negative vs equivocal).

11.4.6 Intra- and Inter-reader Reliability Assessments

A subset of each central reader's ^{64}Cu-SAR-BBN PET/CT scans will be evaluated twice to assess the reproducibility of the readings and consistency among readers.

The intra-reader variability of each reader will be assessed by calculating percent agreement (concordance) and Cohen's pairwise kappa statistics along with the 95% CIs for the dichotomous results for all participants with two scan interpretations.

For inter-reader variability, the agreement among the three independent readers will be assessed by calculating percent pairwise concordance and Fleiss's overall multi-assessor kappa statistics and its 95% CIs.

11.4.7 Biodistribution Analysis

Biodistribution measures of ^{64}Cu-SAR-BBN including maximum and mean SUVs in lesions, visceral/soft tissues, bone, and lesion-to-background ratios will be summarized descriptively for the Biodistribution Analysis Set.

11.5 Interim Analysis

There is no interim analysis planned for this study.

11.6 Handling of Missing Data

Exploratory sensitivity analyses of the primary endpoints will be performed using participants who had evaluable composite Reference Standard data. Additional sensitivity analyses based on all participant in the FAS using the worst case imputation method and tipping point analysis will also be performed to examine the impact of missing or unevaluable composite Reference Standard data. These methods are described in detail in Section 11.4.5.1.

12 STUDY ADMINISTRATION AND RESPONSABILITIES

12.1 General Investigator Responsibilities

The Investigator must ensure that:

- He or she will personally conduct or supervise the study;
- His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the protocol specific Study Personnel Responsibility/Signature Log;
- The study is conducted according to the protocol and all applicable regulations;
- The protection of each participant's rights and welfare is maintained;
- Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each participant before conducting study procedures. If a participant withdraws permission to use protected health information, the Investigator will obtain a written request from the participant and will ensure that no further data will be collected from the participant;
- The consent process is conducted in compliance with all applicable regulations and privacy acts;
- The IRB complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study;
- Any amendment to the protocol is submitted promptly to the IRB;
- Any significant protocol deviations are reported to the Medical Monitor, the Sponsor, and the IRB according to the guidelines at each study site;
- Electronic case report form pages are completed within 5 days of each participant's visit (unless required earlier for SAE reporting);
- All SAEs and pregnancies are reported to the Sponsor or designee within 24 hours of knowledge and to the IRB per IRB requirements;
- All safety reports are submitted promptly to the IRB, as per IRB requirements.

12.2 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

12.3 Compliance with Ethical and Regulatory Guidelines

The Investigator will ensure that this study is conducted in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a USA Investigational New Drug (IND) application, the Investigator will ensure adherence to the basic principles of GCP as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, 1998; and 21 CFR, Part 56, 1998.

This study is also subject to and will be conducted in accordance with 21 CFR, Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

Because this is a "covered" clinical study, the Investigator will ensure adherence to 21 CFR, Part 54, 1998; a covered clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub Investigator in the study. The Investigator or sub Investigator agrees to notify the Sponsor of any change in reportable financial interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last participant has completed the protocol-defined activities.

12.4 Institutional Review Board

This protocol and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter from the IRB to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval. A signed protocol approval page, a letter confirming IRB approval of the protocol and informed consent, and a statement that the IRB is organized and operates according to GCP and the applicable laws and regulations must be forwarded to the Sponsor before screening participants for the study. Additionally, study sites must forward a signed Form FDA 1572 (Investigator Obligation Form) to the Sponsor before screening participants for study enrollment.

Any modifications or amendments made to the protocol or ICF after receipt of the initial IRB approval must also be submitted to the IRB for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the participants may be initiated prior to IRB approval. In that event, the Investigator must notify the IRB, the Medical Monitor, and the Sponsor in writing within 5 working days after implementation. If a change to the protocol in any way increases the risk to the participant or changes the scope of the study, then written documentation of IRB approval must be received by the Sponsor before the amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to participants already actively participating in the study, and they must read, understand, and sign any revised informed consent document confirming willingness to remain in the study.

The Investigator must ensure that all local regulations and reporting requirements to the IRB are met.

12.5 Informed Consent Process

Note: All references to "participant" in this section refer to the study participant or his legally authorized representative.

The Sponsor (or its designee) will provide Investigators with multicenter ICFs for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part

50.25). The final ICFs must be accepted by the Sponsor and approved by the IRB. Investigators must provide the Sponsor with an unsigned copy of the final ICFs before and after it is approved by the IRB. If any new information becomes available that might affect participants' willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each participant must sign and date an IRB-approved ICF written in a language the participant can understand. The ICF should be as nontechnical as practical and understandable to the participant. The ICF must provide the participant with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the participant's personal information and personal health information for purposes of conducting the study. The ICF will include details of the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to their further medical care. Before informed consent is obtained, the participant should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the participant.

Once signed, the original ICF will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the participant's case history. All participants will receive a copy of their signed and dated ICF.

If the ICF is revised during the study and requires the participant to be re consented, informed consent will be obtained in the same manner as for the original ICF.

12.6 Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of all participants during this clinical study. However, because of the experimental nature of this investigational product, the Investigator agrees to allow the IRB, representatives of the Sponsor and its designated agents, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study site records of all participants enrolled into this study. This includes providing by fax, e-mail, or regular mail de-identified copies of clinical, laboratory, ECG, radiology, pathology, and/or other test results when requested by the Sponsor. A statement to this effect will be included in the ICF and a permission form authorizing the use of protected health information will also be included.

In accordance with local and national participant privacy regulations, the Investigator or designee must explain to each participant that in order to evaluate study results, the participant's protected health information obtained during the study may be shared with IRBs, the Sponsor and its designees, and regulatory agencies. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each participant. If a participant withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the participant and to ensure that no further data will be collected from the participant. Any data collected on the participant before withdrawal will be used in the analysis of study results. The Sponsor will only use or disclose the participant's protected health information consistent as defined in the ICF.

The Investigator must assure that each participant's anonymity will be strictly maintained, and that each participant's identity is protected from unauthorized parties. Only participant initials,

date of birth, and an identification code (but no participant names) should be recorded on any form or biological sample submitted to the IRB, to the Sponsor or its designees (e.g., laboratories), or to regulatory authorities. However, sufficient information must be retained at the study site to permit sample data and data in the database to be connected with the unique participant number assigned to each study participant.

The Investigator agrees that all information received from the Sponsor, including, but not limited to, the investigational product, the IB, this protocol, the eCRFs, and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

12.7 Study Files and Retention of Records and Biological Samples

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified by the IRB, representatives of the Sponsor and its designated agents, and authorized employees of appropriate regulatory agencies. These documents should be classified into at least the following 2 categories: Investigator's study file and participant clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB and governmental approval with correspondence, signed ICF, drug accountability records, staff curriculum vitae and authorization forms (e.g., Form FDA 1572), and other appropriate documents and correspondence pertaining to the conduct of the study.

The required source data referenced in the monitoring plan for the study should include sequential notes containing at least the following information for each participant:

- Participant identification (name, date of birth, sex, race and ethnicity);
- Documentation that participant meets each of the eligibility criteria, e.g., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in study (including study number);
- Study discussed and date of informed consent/re-consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of investigational products (including relevant drug dispensing information);
- Record of all AEs and other safety parameters (including start and end date, causality, and severity (intensity));
- Concomitant medications (including start and end date and dose if relevant dose changes occur);
- Date of study completion and reason for discontinuation, if applicable.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (the United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified or for 15 years, whichever is longer. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor and obtain written approval from the Sponsor before destroying any clinical study records. The Investigator will promptly notify the Sponsor in the event of accidental loss or destruction of any study records. The Sponsor will inform the Investigator of the date that study records may be destroyed or returned to the Sponsor.

The Sponsor must be notified in advance and must provide express written approval of any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the participant, appropriate copies should be made for storage outside of the study site.

Biological samples retained by the Investigator will be stored and maintained by the Investigator until notification is received from the Sponsor that the retained samples and records no longer need to be retained. The Investigator must obtain written permission from the Sponsor before disposing of any retained samples. The Investigator should promptly notify the Sponsor in the event of accidental loss or destruction of any study samples. With the permission of the Sponsor, the retained samples may be transferred to an acceptable designee, such as another Investigator, another institution, a contract storage site, or to the Sponsor.

12.8 Participant Screening Log

The Investigator must keep a record that lists all participants who signed the ICF (including those who did not undergo screening assessments). For those participants who declined to participate, post signing the ICF or were subsequently excluded from enrollment, the reasons for not enrolling in the study must be described.

12.9 Modifications of the Protocol or Informed Consent Documents

Protocol modifications, except those intended to reduce immediate risk to study participants, will be made only by the Sponsor. All protocol modifications must be submitted to the IRB in accordance with local requirements. Except as noted in Section 12.4, IRB approval must be obtained before changes can be implemented.

The ICF cannot be changed without prior written approval by the Sponsor and the study site's IRB.

The Sponsor may not reimburse the Investigator for cases in which study procedures and evaluations are not conducted in line with the IRB approved protocol.

12.10 Case Report Forms

Authorized study site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled participant, with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes, study site charts, or other study-specific source documents). The Investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each participant's visit (unless required earlier for SAE reporting). The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those participants who fail to complete the study (even during the screening period). If a participant withdraws from the study, the reason must be noted on the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system. After the Investigator or the Investigator's designees (e.g., research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the principal Investigator or sub-Investigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

12.11 Clinical Monitoring

Representatives of the Sponsor or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and study site staff as well as any appropriate communications by mail, e-mail, or telephone. The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data.

In accordance with GCP, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.12 Inspections

The source documents for this study must be made available to appropriately qualified personnel from the Sponsor or its representatives, to the IRB, and to regulatory authority or health authority inspectors as a part of their responsibility to protect human participants in research. The Investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit to representatives of the Sponsor and regulatory agencies. It is important that the Investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor immediately.

12.13 Data Management

Electronic data capture will be used to enter study data eCRFs and to transfer the data into a study-specific electronic database. Instances where the eCRF captured data are considered source data will be outlined in separate study specific documentation. During the data collection process, automated quality assurance programs will be used to identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative study site for resolution. As appropriate, eCRFs, listings, tables, and SAS datasets will be provided to the study sites for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide an audit trail, security mechanisms, and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access to only data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study sites and at the Sponsor or its designee. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured when not under review.

12.14 Clinical Study Insurance

The Sponsor will secure clinical study insurance. An insurance certificate will be made available to the participating study sites before study initiation.

12.15 Communications with Regulatory Authorities

The Sponsor, working either directly or through designees, will assume responsibility for regulatory interactions with relevant regulatory authorities. The Sponsor will maintain an IND application for the investigational product in support of the study in the United States and will maintain similar regulatory applications with other regulatory authorities as required for conduct of the study. In fulfilling this responsibility, the Sponsor (or a designee) will collect, assemble, and communicate all required regulatory documents (e.g., Form FDA 1572, Investigator financial disclosure forms, protocol and protocol amendments, IB, informed consent documents, annual reports) as required by regulation. The Sponsor (or a designee) will also assume responsibility for safety reporting to regulatory authorities as described in Section 10.5.

12.16 Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a participant's medical records) are the sole property of Sponsor.

For clinical interventional studies in patients, Sponsor will post study results on websites such as https://clinicaltrials.gov/ in accordance with FDA reporting rules.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.17 Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The Investigator will be responsible for notifying the relevant study site's IRB. The Sponsor will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the participants' interests. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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13 INVESTIGATOR AGREEMENT

Protocol Number: CLB03

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

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for GCP, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act, and local regulatory guidelines. I will attempt to complete the study within the time designated. I will ensure that the rights, safety, and welfare of participants under my care are protected. I will ensure control of the drugs under investigation in this study. I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all participant information (case report forms, shipment and drug return forms, and all other information collected during the study) and drug disposition in accordance with FDA regulations. I will not enroll any participants into this protocol until IRB approval and Sponsor approval are obtained.

_____

Site or Institution Name

_____

Site number

_____

Investigator Name (Print)

_____ _____

Investigator Signature Date