PROTOCOL SYNOPSIS

Protocol Number	CLP04
Investigational Product	^{64}Cu-SAR-bisPSMA
Protocol Title	Positron Emission Tomography using ^{64}Cu-SAR-bisPSMA in participants with high-risk prostate cancer prior to radical prostatectomy: A prospective, single-arm, multi-center, blinded-review, Phase 3 diagnostic performance study
Short Title	CLARIFY
Phase	Phase 3
IND Number	158388
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 ^{64}Cu-SAR-bisPSMA administered to participants with untreated, histopathology-confirmed prostate cancer (PC), with high-risk features, who are proceeding to radical prostatectomy (RP) with pelvic lymph node dissection (PLND). Participants who provide informed consent will undertake screening visit(s) (Visit 1) to determine their eligibility to participate in the study. The maximum screening period is 28 days and will include institutional Standard of Care (SOC) imaging work up (e.g., magnetic resonance imaging [MRI], computed tomography [CT], approved SOC prostate specific membrane antigen [PSMA] positron emission tomography [PET]/CT). Eligible participants will receive a single administration of 200 MBq of ^{64}Cu-SAR-bisPSMA on Day 1 (Visit 2), followed by a PET/CT scan mid-thigh to the skull vertex at 1 to 4 hours post dose (denoted as "Day 1 PET") and at 24 ±6 hours post dose (denoted as "Day 2 PET", Visit 3). Safety assessments will be completed following the administration of ^{64}Cu-SAR-bisPSMA on Day 1, Day 2 and on Day 7 ±4 days (Visit 4) via a telephone call to capture any late-occurring adverse events (AEs). After completion of Visit 4, participants will proceed to RP with PLND. The specimens from the surgery will be processed and analyzed locally. The local pathologist evaluating the samples will be blinded to the ^{64}Cu-SAR-bisPSMA PET/CT scans/results. The histopathology results will be recorded within 90 days of Day 1 (End of Study). The screening institutional SOC imaging will be interpreted by a single independent, blinded, central reader without access to the ^{64}Cu-SAR-bisPSMA PET/CT scans. The Day 1 and Day 2 ^{64}Cu-SAR-bisPSMA PET/CT scans will be interpreted locally and by three independent, blinded, central readers. Each reader will assess the scans visually for the presence of abnormal ^{64}Cu-SAR-bisPSMA uptake in the pelvic lymph nodes (LNs), prostate gland, extra-pelvic LNs, visceral/soft tissue and bone. If distant metastatic disease (lesion[s] within the extra-pelvic LNs, bone or visceral/soft tissue regions) is detected on the ^{64}Cu-SAR-bisPSMA PET/CT per the local interpretation of the scans, histopathology (from image-guided biopsy or surgery) should be obtained if clinically feasible. This study will include a Pharmacokinetic Substudy. For study design and applicable participant inclusion criteria, refer to relevant sections in the body of Protocol.

Primary Objective	**Primary Endpoints**
To assess the diagnostic performance of ^{64}Cu-SAR-	Independent primary endpoints for Day 1 and Day 2 PET:

bisPSMA PET to detect regional nodal metastases.	• Co-primary endpoint of sensitivity and specificity of ^{64}Cu-SAR-bisPSMA PET to detect PC within the pelvic LNs compared to the Standard of Truth (SOT).

Abbreviations: LN=lymph node; PET=positron emission tomography; PC=prostate cancer; SOT=Standard of Truth

Secondary Objectives	**Secondary Endpoints**
To investigate the safety and tolerability of ^{64}Cu-SAR-bisPSMA.	Incidence and severity of treatment-emergent AEs and SAEs following administration of ^{64}Cu-SAR-bisPSMA.
To assess the consistency of ^{64}Cu-SAR-bisPSMA PET/CT interpretations for the three central readers.	Inter-reader reliability of agreement estimated with a multiple-reader kappa statistic.
To assess the PPV and NPV of ^{64}Cu-SAR-bisPSMA PET to detect PC within the pelvic LNs.	Reported independently for Day 1 and Day 2 PET: • PPV and NPV of ^{64}Cu-SAR-bisPSMA PET to detect PC within the pelvic LNs compared to the SOT.
To assess the ability of ^{64}Cu-SAR-bisPSMA PET to detect PC.	Reported independently for Day 1 and Day 2 PET: • Sensitivity of ^{64}Cu-SAR-bisPSMA PET to detect PC within the prostate, pelvic LNs, extra-pelvic LNs, bone and visceral/soft tissue regions compared to the SOT.
To assess the ability of ^{64}Cu-SAR-bisPSMA PET to detect primary PC.	Reported independently for Day 1 and Day 2 PET: • Sensitivity of ^{64}Cu-SAR-bisPSMA PET to detect PC within the prostate gland compared to the SOT.
To assess the diagnostic performance of ^{64}Cu-SAR-bisPSMA PET to detect regional nodal metastases without subregion matching.	Reported independently for Day 1 and Day 2 PET: • Sensitivity and specificity of ^{64}Cu-SAR-bisPSMA PET to detect PC within the pelvic LNs compared to the SOT, without the requirement of subregion (Left or Right) matching between ^{64}Cu-SAR-bisPSMA PET and SOT.
To determine the dosimetry, PK and excretion of ^{64}Cu-SAR-bisPSMA in participants in the PK Substudy.	The following parameters will be expressed from the PET scans: • Absorbed dose (mGy/MBq) in organs. • Effective dose (mSv/MBq). The following parameters will be expressed from blood: • Radioactivity concentration per collection time (MBq/mL), maximum concentration, AUC_{0-t}, AUC_{0-inf}, kel, CL, Vz, T_{max} and $t_{1/2e}$. • Ratios of blood-to-plasma radioactivity at each time point/per participant. • Metabolic profiles (via high-performance liquid chromatography). The following parameters will be expressed from urine: • Radioactivity concentration per collection time (MBq/mL), $Ae_{interval}$, T_{Rmax}, R_{max}, Ae_{0-t}, $\%Fe_{0-t}$. • Metabolic profiles (via high-performance liquid chromatography).

Abbreviations: $\%Fe_{0-t}$=percent of total dose recovered in urine; AE=adverse event; Ae_{0-t}=cumulative amount of excreted radioactivity from time zero to the last collection interval; $Ae_{interval}$=total amount of excreted radioactivity per urine collection interval; AUC_{0-inf}=area under the (activity-time) curve from time of dose administration to infinity; AUC_{0-t}=area under the (activity-time) curve from time of dose to last measurable concentration; CL=total clearance; CT=computed tomography; kel=terminal elimination rate constant; LN=lymph node; MBq= megabecquerel; mGy= milligray; mL= milliliter; mSv= millisievert; NPV=negative predictive value; PET=positron emission tomography; PC=prostate cancer; PK=pharmacokinetic; PPV=positive predictive value; R_{max}=rate max; SAE=serious adverse event; SOT=Standard of Truth;

$t_{1/2e}$=elimination half-life; T_{max}=time to reach the maximum concentration; T_{Rmax}=midpoint of the collection interval associated with the maximum observed excretion rate; Vz=total volume of distribution

Exploratory Objectives	Exploratory Endpoints
To compare the diagnostic performance of ^{64}Cu-SAR-bisPSMA PET to detect extra-prostatic PC to that of the baseline SOC imaging.	Reported independently for Day 1 and Day 2 PET: • Number and percentage of participants who are SOC imaging pelvic LN negative, but ^{64}Cu-SAR-bisPSMA PET pelvic LN positive and histopathology positive. • Number and percentage of participants who are ^{64}Cu-SAR-bisPSMA PET pelvic LN positive but SOC imaging pelvic LN negative and histopathology negative. • Number and percentage of participants who are SOC PSMA PET pelvic LN negative, but ^{64}Cu-SAR-bisPSMA PET pelvic LN positive and histopathology positive. • Number and percentage of participants who are ^{64}Cu-SAR-bisPSMA PET pelvic LN positive but SOC PSMA PET pelvic LN negative and histopathology negative. • Percentage of participants upstaged to N1 or M1 based on the ^{64}Cu-SAR-bisPSMA PET compared to the SOC imaging. • Percentage of participants upstaged to N1 or M1 based on the ^{64}Cu-SAR-bisPSMA PET and confirmed as true positive by histopathology compared to the SOC imaging. • Percentage of participants upstaged to N1 or M1 based on the ^{64}Cu-SAR-bisPSMA PET compared to the SOC PSMA PET. • Percentage of participants upstaged to N1 or M1 based on the ^{64}Cu-SAR-bisPSMA PET and confirmed as true positive by histopathology compared to the SOC PSMA PET. • Sensitivity and specificity of ^{64}Cu-SAR-bisPSMA PET compared to the SOC PSMA PET (overall and by tracer) to detect PC within the pelvic LNs compared to the SOT. • PPV and NPV of ^{64}Cu-SAR-bisPSMA PET compared to the SOC PSMA PET (overall and by tracer) to detect PC within the pelvic LNs compared to the SOT.
To assess the ability of ^{64}Cu-SAR-bisPSMA PET to detect distant metastatic disease (based on local assessment only).	Reported independently for Day 1 and Day 2 PET: • PPV of ^{64}Cu-SAR-bisPSMA PET to detect distant metastatic PC within the extra-pelvic LNs, bone and visceral/soft tissue regions compared to the SOT.
To assess the number and location of lesion(s) detected on ^{64}Cu-SAR-bisPSMA PET compared to baseline SOC imaging.	Reported independently for Day 1 and Day 2 PET: • Number of lesions detected per participant and per region (prostate gland, pelvic LNs, extra-pelvic LNs, bone, visceral/soft tissue) on ^{64}Cu-SAR-bisPSMA PET compared to SOC imaging. • Number of lesions detected per participant and per region (prostate gland, pelvic LNs, extra-pelvic LNs, bone, visceral/soft tissue) on ^{64}Cu-SAR-bisPSMA PET compared to SOC PSMA PET.
To compare the detection of Day 1 and Day 2 ^{64}Cu-SAR-bisPSMA PET.	Difference in the total number of lesions detected per participant on Day 1 and Day 2.
To explore the correlation between ^{64}Cu-SAR-bisPSMA PET-positivity and true/false positivity.	Reported independently for Day 1 and Day 2 PET: • Relationship between PET-positivity (SUV, TBR), versus true/false positivity, and as a function of region and size.
To explore the correlation between ^{64}Cu-SAR-bisPSMA PET-positivity and aggressiveness of the disease.	Reported independently for Day 1 and Day 2 PET: • Relationship between PET-positivity (SUV, TBR) and International Society of Urological Pathology (ISUP) Grade from the prostatectomy and pelvic LN dissection specimens.

To compare lesion biodistribution and size parameters on Day 1 and Day 2 ^{64}Cu-SAR-bisPSMA PET with SOC PSMA PET.	Reported independently for Day 1 and Day 2 PET: • Comparison of SUV and TBR for ^{64}Cu-SAR-bisPSMA PET versus SOC PSMA PET. • Comparison of lesion sizes detected on ^{64}Cu-SAR-bisPSMA PET versus SOC PSMA PET.

Abbreviations: LN=lymph node; PC=prostate cancer; PET=positron emission tomography; PPV=positive predictive value; PSA=prostate-specific antigen; SOC=standard of care; SOT=Standard of Truth; SUV=standardized uptake value; TBR=tumor-to-background ratio

Number of Participants Planned	Main Study: 325 PK Substudy: Approximately 20
Target Population	The target population for the Main Study is untreated patients with a histopathology-confirmed diagnosis of PC with high-risk features, who are proceeding to RP with PLND. The target population for the PK Substudy is patients with PC.
Inclusion Criteria	**Main Study:** 1. At least 18 years of age. 2. Signed informed consent. 3. Untreated (i.e. no therapy for PC, including no androgen deprivation therapy of any duration), histologically confirmed adenocarcinoma of the prostate. 4. High-risk or greater PC defined by National Comprehensive Cancer Network Guidelines Version 1.2023 (clinical stage ≥T3a, or Grade Group ≥4, or prostate-specific antigen >20 ng/mL). 5. Patients electing to undergo RP with PLND. 6. For patients who have partners of childbearing potential: partner and/or patient must use a method of birth control with adequate barrier protection. **PK Substudy:** 1. At least 18 years of age. 2. Signed informed consent. 3. Diagnosis of PC. 4. For patients who have partners of childbearing potential: partner and/or patient must use a method of birth control with adequate barrier protection.
Exclusion Criteria	**All Participants:** 1. Administration of any high energy (>300 KeV) gamma-emitting radioisotope within 5 physical half-lives prior to Day 1. 2. Known or expected hypersensitivity to ^{64}Cu-SAR-bisPSMA or any of its components. 3. Patients with known predominant small cell or neuroendocrine PC. 4. History of other active malignancy within 3 years prior to Day 1, except for adequately treated non-melanoma skin cancer and superficial bladder tumors. 5. 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 (IP) administered in this study is ^{64}Cu-SAR-bisPSMA. ^{64}Cu-SAR-bisPSMA has three basic components: (a) the radionuclide (copper-64) chelated by (b) bisCOSAR (a bifunctional metal chelator) which is linked to (c) two urea based small molecule inhibitors of PSMA. 200 MBq of ^{64}Cu-SAR-bisPSMA will be administered as a single bolus intravenous (IV) injection at Day 1.
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.