A Multi-Center, Open-Label, Randomized Phase 1/2 Study of Copper Cu 64 PSMA I&T Injection in Patients with Histologically Proven Metastatic Prostate Cancer

Study Number: CURCu64PSM0001

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADT	Androgen deprivation therapy
AE	Adverse event
AR	Androgen receptor
C-11	Carbon-11
CDR	Correct detection rate
CFR	Code of Federal Regulations
CLR	Correct localization rate
ClCr	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cu-64	Copper-64
CV	Curriculum Vitae
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
F-18	Fluorine-18
FDA	Food and Drug Administration
Ga-68	Gallium-68
GCP	Good Clinical Practice
I&T	Imaging and Therapeutic
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICL	Imaging Core Laboratory
ID	Injected dose
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IME	Imaging evaluable
ITE	Intent to evaluate
LNM	Lymph node metastases
MBq	Megabecquerel
mCi	Millicurie
mCRPC	Metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MIRD	Committee on Medical Internal Radiation Dose
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PC	Prostate cancer
PET	Positron Emission Tomography
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
ROI	Regions of interest
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SOP	Standard Operating Procedure
SUV_{max}	Maximum standard uptake value
UP	Unanticipated problem
US	United States
VOI	Volume of interest
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title of Study	A Multi-Center, Open-Label, Randomized Phase 1/2 Study of Copper Cu 64 PSMA I&T Injection in Patients with Histologically Proven Metastatic Prostate Cancer
Phase of Clinical Trial	Phase 1/2
Indication	Detection and localization of recurrent prostate cancer in men with biochemical recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.
Number of Sites	5-10
Drug Product	Copper Cu 64 PSMA I&T
Study Objectives	**Phase 1** **Primary Objectives:** The primary objectives of the Phase 1 portion of this study are: 1. To assess the safety and determine radiation dosimetry estimates following intravenous administration of 5, 7, and 9 mCi doses of copper Cu 64 PSMA I&T injection in patients with recurrent prostate cancer. Safety will be assessed by monitoring adverse events, clinical chemistry, hematology, urinalysis, vital signs, ECG, and determination of radiation absorbed dose estimates. 2. To assess the PET/CT image quality following intravenous administration of 5, 7, and 9 mCi doses of copper Cu 64 PSMA I&T injection to determine an acceptable dose for obtaining diagnostic quality PET/CT images. **Phase 2** **Primary Objectives:** The primary objectives of the Phase 2 portion of this study are: 1. To determine the region-level correct localization rate (CLR) of copper Cu 64 PSMA I&T injection PET/CT imaging for the detection of recurrent metastatic prostate cancer at 1 hour and 4 hours post injection. The CLR is defined as the percentage of regions containing at least one true PET positive lesion, with exactly localized correspondence between PET/CT imaging and the Composite Reference Standard regardless of any co-existent false positive findings, within the same region, out of all regions containing at least one PET positive finding.

	2. To determine the patient-level correct detection rate (CDR) of copper Cu 64 PSMA I&T injection PET/CT imaging for the detection of recurrent metastatic prostate cancer at 1 hour and 4 hours post injection. The CDR is defined as the percentage of patients who have at least one true PET positive lesion, with exactly localized correspondence between PET imaging and the Composite Reference Standard, regardless of any co-existent false positive findings, out of all patients who are scanned. 3. To assess the safety of copper Cu 64 PSMA I&T injection in patients with recurrent prostate cancer. Safety will be assessed by monitoring adverse events, clinical chemistry, hematology, urinalysis, ECG, and vital signs. **Secondary Objective:** 1. To compare the diagnostic quality of PET/CT images obtained at 1 hour and 4 hours post copper Cu 64 PSMA I&T injection.
Study Design	This is a prospective, open-label Phase 1/2 study to evaluate copper Cu 64 PSMA I&T injection for PET/CT imaging in patients with recurrent metastatic prostate cancer after radical prostatectomy or radiation therapy. **Phase 1** The Phase 1 portion of the study will include a total of 12 patients with metastatic prostate cancer. Patients will be randomized into three groups of four patients. Patients in each group will receive a single intravenous dose of 5, 7, or 9 mCi of copper Cu 64 PSMA I&T. Whole-body PET/CT images will be acquired at 1 hour ± 15 minutes, 4 hours ± 0.5 hours, and 24 hours ± 2.0 hours post-injection to determine radiation absorbed dose estimates. The 1 hour and 4-hour PET/CT images will be evaluated independently by three readers blinded to all patient information and dose administered to assess the quality of the images (24 PET/CT image sets total). The assessments will be used to determine an acceptable dose to be administered for the Phase 2 study. **Phase 2** The Phase 2 portion of the study will include a separate group of 26 patients with metastatic prostate cancer. Each patient will be administered the same intravenous dose of copper Cu 64 PSMA I&T injection determined in the Phase 1 study. PET/CT images will be acquired for all patients at 1 hour ± 15 minutes and 4 hours ± 30 minutes post copper Cu 64 PSMA I&T injection. The PET/CT images will be interpreted independently by three readers blinded to all patient information. Each patient study will be assessed and scored for the detection of prostate cancer. Specifically, each reader will categorize images as “Disease” or “No Disease” based only on tumor

	uptake of copper Cu 64 PSMA-I&T in each of the four regions: 1) prostate bed or prostate gland, 2) lymph nodes (pelvic and extra pelvic), 3) bone, and 4) viscera/soft tissue. Analysis of the reads will be used for determination of the CLR and CDR for 1 hour and 4-hour post-injection imaging of copper Cu 64 PSMA I&T PET/CT by comparison to the Composite Reference Standard.
Study Population	The study will include patients with metastatic proven prostate adenocarcinoma. **Phase 1**: Total of 12 patients. ***Inclusion Criteria:*** 1. Patients with histologically proven prostate adenocarcinoma. 2. Prior radical prostatectomy or radiation therapy with curative intent. 3. Recurrence of disease, defined as: a. Prior Radical Prostatectomy: PSA > 0.2 ng/mL, or b. Prior Radiation Therapy: 2 ng/mL rise in PSA over post-treatment nadir. 4. Patients with at least one extraprostatic site of disease suspected based on prior imaging or diagnosed by biopsy. 5. Age greater than or equal to 18 years. 6. Able to understand and provide signed written informed consent. ***Exclusion Criteria:*** 1. Body weight greater than 350 lb. (158 kg). 2. Investigational therapy within the past 30 days. 3. Creatinine clearance (ClCr) less than 30 mL/min. 4. Participants who are capable of fathering a child and who are unwilling to take precautions to prevent pregnancy. **Phase 2:** Total of 26 patients. ***Inclusion Criteria:*** 1. Patients with histologically proven prostate adenocarcinoma. 2. Prior radical prostatectomy or radiation therapy with curative intent. 3. Recurrence of disease defined as: a. Prior Radical Prostatectomy: PSA > 0.2 ng/mL, or

	b. Prior Radiation Therapy: 2 ng/mL rise in PSA over post-treatment nadir 4. Patients with at least one extraprostatic site of disease suspected based on prior imaging or diagnosed by biopsy. 5. Age greater than or equal to 18 years. 6. Able to understand and provide signed written informed consent. ***Exclusion Criteria:*** 1. Androgen deprivation therapy (ADT) or other therapies targeting the androgen pathway unless subject has a rising PSA level. 2. Body weight greater than 350 lb (158 kg). 3. Investigational therapy within the past 30 days. 4. Creatinine clearance (ClCr) less than 30 mL/min. 5. Participants who are capable of fathering a child and who are unwilling to take precautions to prevent pregnancy.
Phase 1 Study Procedures	A total of 12 patients will be randomly assigned to one of three groups, four patients per group, to receive a single intravenous injection of 5, 7, or 9 mCi of copper Cu 64 PSMA I&T. ***Screening:*** All patients will be screened to ensure they meet all inclusion and no exclusion criteria for enrollment in the study. Written informed consent will be obtained for all patients enrolled in the study. ***Baseline Assessments:*** Routine clinical chemistry, hematology, and urinalysis will be obtained for all patients prior to dosing. PSA will also be obtained for all patients prior to dosing. Medical history and physical examination will be performed prior to dosing. This will include information on the history of the prostate cancer. Concomitant medication history will also be obtained. A baseline 12-lead ECG will be obtained prior to dosing. Vital signs including heart rate, respiratory rate, and blood pressure will be assessed prior to dosing. ***Randomization:*** Patients will be randomized to receive a single dose of 5, 7 or 9 mCi of copper Cu 64 PSMA I&T injection.

	Pharmacokinetic/Radiation Absorbed Dose: Whole body PET/CT scans will be acquired at 1 hour ± 15 minutes, 4 hours ± 30 minutes, and 24 hours ± 2.0 hours post-injection. CT scans will be acquired for attenuation correction and anatomical reference. Images will be acquired using calibrated time-of-flight mode using digital scanners. For calculation of radiation absorbed dose estimates, volumes of interest (VOI) will be delineated for the kidneys, liver, lungs, spleen, urinary bladder, salivary glands, and total body. Image count values will be corrected for radioactive decay, scanner response, start/stop times, and net injected dose. The remaining activity will be assumed to be distributed homogeneously throughout the body after adjusting for activity in the organs, blood, and voided urine. Organ-specific and whole-body radiation dose analysis will be performed using OLINDA/EXM software, following Medical Internal Radiation Dose (MIRD) guidelines. Voided urine activity values will be accounted for in the dosimetry analysis by collection of all urine for 0-1 hour and 1-4 hour intervals post-injection. The total voided urine volume for each interval will be measured and the total radioactivity calculated by comparison to a calibrated standardized sample or per Site's standard methods. Calibrated urine voiding curves will be determined and included in the dosimetry analysis. Venous blood samples will be collected prior to copper Cu 64 PSMA I&T injection and at 1 hour, 2 hours, 4 hours and 24 hours post-injection. The radioactivity concentration in the blood samples will be determined on a per-milliliter basis using a calibrated standard measured in a well counter for dosimetry analysis or per Site's standard methods. No metabolite analysis will be performed on the blood or urine samples. Estimates of radiation absorbed dose will be calculated for all patients with the data from the VOI analysis at each imaging timepoint. ***Dose-Range Evaluation:*** The 1 hour and 4-hour post-injection PET/CT images for all patients will be evaluated for diagnostic image quality by three independent readers blinded to all patient information and doses administered. Image quality will be assessed using the following scoring system: 0 = inadequate (grainy images with poor delineation of lesions); 1 = questionable (clear images, but lesion delineation is suboptimal and small lesions [1 cm] are hard to assess); 2 = acceptable (clear images, large and small lesion delineation is possible). Cohort scores will be calculated by adding the average patient image scores in each dosing group. In addition, the blinded readers will record lesion signal-to-noise, Maximum Standard Uptake Value (SUV_{max}), lesion-contrast-to-noise and lesion-to-normal tissue values derived from VOI values as described in the Independent Reader Manual. The cohort scores and image quality

	evaluations will be used in the determination of the injected dose value for the Phase 2 study. ***Safety Assessments:*** All patients will be followed for adverse events for 24 hours post-injection. Severity of adverse events will be assessed independently by the Investigators and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, in which Grades 1, 2, 3, 4, and 5 describe adverse events as mild, moderate, severe, or medically significant but not life-threatening, life-threatening, and death related to adverse event, respectively. Routine clinical chemistry, hematology, PSA, and urinalysis will be performed at 4 hours post-injection on all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, they will be reassessed at 24 hours post-injection and followed until values return to normal or baseline, or until the Investigator and Medical Monitor determine it is no longer necessary. A 12-lead ECG will be obtained at 30 minutes and 3.5 hours post-injection for all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, the patient will be reassessed at 24 hours post-injection and followed until values return to normal or baseline, or until the Investigator and Medical Monitor determine it is no longer necessary. Vital signs including heart rate, blood pressure, and respiratory rate will be obtained at 5 minutes, 30 minutes, 1 hour and 4 hours post-injection on all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, they will be reassessed at 24 hours post-injection. ***Follow-up:*** Patients will be seen 24 hours post-injection for assessment of adverse events, clinically significant lab or ECG values or clinically significant vital signs. Patients with clinically significant changes will be followed until such events resolve or as decided by the Investigator and Medical Monitor.

Phase 2 Study Procedures	A total of 26 patients will be included in the Phase 2 portion of the study. ***Screening:*** All patients will be screened to ensure they meet all inclusion and no exclusion criteria for enrollment in the study. Written informed consent will be obtained for all patients enrolled in the study.

	Baseline Assessments: Routine clinical chemistry, hematology, and urinalysis will be obtained for all patients prior to dosing. PSA will also be obtained for all patients prior to dosing. Medical history and physical examination will be performed prior to dosing. This will include information on the history of the prostate cancer. Concomitant medication history will also be obtained. ***Imaging Procedure:*** All patients will undergo PET/CT imaging at 1 hour ± 15 minutes and 4 hours ± 30 minutes following copper Cu 64 PSMA I&T injection using the dose determined in Phase 1. The 1 hour and 4-hour images will be independently read by three experienced blinded readers for the detection of prostate cancer. Specifically, each reader will categorize images as "Disease" or "No Disease" based only on tumor uptake of copper Cu 64 PSMA-I&T in each of the four regions: 1) prostate bed or prostate gland, 2) lymph nodes (pelvic and extra pelvic), 3) bone, and 4) viscera/soft tissue. ***Efficacy Analysis:*** ***Composite Reference Standard*** All patients will undergo an efficacy assessment based on copper Cu 64 PSMA I&T PET/CT results and the results of clinical presentation for evaluation against the Composite Reference Standard. The Composite Reference Standard is defined as follows: 1. Local histopathology obtained from prostate cancer surgery or biopsy obtained within 60 days before or following copper Cu 64 PSMA I&T PET/CT, or 2. If histopathology is not available, anatomical correlation of conventional image findings (e.g., targeted MRI or CT or any FDA-approved PET PSMA agent) that are acquired prior to locoregional or systemic treatment and within 60 days before or following copper Cu 64 PSMA I&T PET/CT ***Safety Assessments:*** All patients will be followed for adverse events for 24 hours post-injection. Severity of adverse events will be assessed independently by the Investigators and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, in which Grades 1, 2, 3, 4, and 5 describe adverse events as mild, moderate, severe or medically significant but not life-threatening, life-threatening, and death related to the adverse event, respectively.

	Routine clinical chemistry, hematology, PSA, and urinalysis will be performed at 4 hours post-injection on all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, they will be reassessed at 24 hours post-injection and followed until values return to normal or baseline, or until the Investigator and Medical Monitor determine it is no longer necessary. A 12-lead ECG will be obtained at 30 minutes and 3.5 hours post-injection for all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, the patient will be reassessed at 24 hours post-injection and followed until values return to normal or baseline, or until the Investigator and Medical Monitor determine it is no longer necessary. Vital signs including heart rate, blood pressure, and respiratory rate will be obtained at 5 minutes, 30 minutes, 1-hour and 4-hour post-injection on all patients. If no clinically significant changes are noted, no additional follow-up will be performed. If significant findings are noted, they will be reassessed at 24 hours post-injection. ***Follow-up:*** Patients will be contacted 24 hours post-injection for assessment of adverse events, clinically significant lab or ECG values or clinically significant vital signs. Patients with clinically significant changes will be followed until such events resolve or as decided by the Investigator and Medical Monitor. Patients will continue to be followed for disease progression by their physician per their standard of care. Any conventional imaging (dedicated CT, MRI, bone scan, or FDA-approved PET/CT) based on the site's clinical Standard of Care (SOC) performed within 12 months of administration may be collected to evaluate disease progression.
Statistical Analysis	***Sample Size:*** **Phase 1:** The sample size for the Phase 1 portion of the study is not powered for hypothesis testing but is an appropriate sample size for calculation of the radiation absorbed dose following administration of copper Cu 64 PSMA I&T injection. In addition, four patients per dose level is an adequate sample to determine the lowest dose level yielding diagnostic quality images at 1- and 4-hours post-injection. This is defined as a three-point assessment of image quality. ***Study Endpoints:*** **Phase 2:** ***Primary Efficacy Endpoints*:**

	1. To determine the region-level correct localization rate (CLR) of copper Cu 64 PSMA I&T injection PET/CT imaging for the detection of recurrent metastatic prostate cancer at 1- and 4-hours post-injection. The CLR is defined as the percentage of regions containing at least one true PET positive lesion, with exactly localized correspondence between PET/CT imaging and the Composite Reference Standard regardless of any co-existent false positive findings, within the same region, out of all regions containing at least one PET positive finding. 2. To determine the patient-level correct detection rate (CDR) of copper Cu 64 PSMA I&T injection PET/CT imaging for the detection of recurrent metastatic prostate cancer at 1 hour and 4 hours post-injection. The CDR is defined as the percentage of patients who have a least one true PET positive lesion with exactly localized correspondence between PET imaging and the Composite Reference Standard regardless of any co-existent false positive findings, out of all patients who are scanned Since all patients enrolled in the study will have disease, the CLR is a measure of the sensitivity of the copper Cu 64 PSMA I&T injection scan. Current methods have a CLR of 60%; thus, the hypothesis to be tested in the Phase 2 portion of the study is: H0: $\pi C = \pi 0$ versus HA: $\pi C > \pi 0$ where πC is the CLR for copper Cu 64 PSMA I&T injection and $\pi 0$ is the CLR from the literature (estimated to be 60%). This hypothesis will be tested using an exact one-sample binomial test with a one-sided $\alpha=0.025$. ***Secondary Objective*:** The secondary objective for the Phase 2 study is to compare the diagnostic quality of PET/CT images obtained at 1 hour and 4 hours post copper Cu 64 PSMA I&T injection. ***Safety Endpoint*:** To assess the safety of copper Cu 64 PSMA I&T injection in patients with recurrent prostate cancer. Safety will be assessed by monitoring adverse events, clinical chemistry, hematology, urinalysis, ECG, and vital signs. ***Analysis Populations*:** Several analysis populations of patients are defined, which may provide a more complete description of the collected data, provide a logical mechanism for grouping and listing results based on an applied analysis, and/or allow appropriate stratification of various analyses. 1. The Enrolled Patient Population (EPP) represents patients who sign an Informed Consent Form and have baseline data.

	2. The Intent-to-Evaluate (ITE) Population are patients in the Enrolled Patient Population who satisfy the eligibility criteria and who have undergone a copper Cu 64 PSMA I&T imaging study. 3. The Imaging Evaluable (IME) Population are patients in the ITE Population who have completed imaging procedures according to the protocol with technically satisfactory results. 4. The Safety Population are patients who are administered copper Cu 64 PSMA I&T injection.