Clinical Study Protocol

STUDY TITLE	A Phase 1/2 open-label, multi-center, safety and tolerability study of a single dose of ^{68}Ga-PSMA-R2 in patients with biochemical relapse (BR) and metastatic prostate cancer (mPCa).
SHORT TITLE	PROfind
INVESTIGATIONAL PRODUCT	Kit for the preparation of ^{68}Ga-PSMA-R2 for injection
STUDY	Safety and Tolerability Study (Phase 1/2)
OBJECTIVES	Assessment of the safety and tolerability of a single administration of 3 mega Becquerel (MBq)/kg, but not less than 150 MBq and not more than 250 MBq, of ^{68}Ga-PSMA-R2, to assess the pharmacokinetics (PK), biodistribution, and dosimetry of ^{68}Ga-PSMA-R2, and to establish the optimal imaging method for determining location and burden of positive lesions in adult male patients with biochemical relapse (BR) and metastatic prostate cancer (mPCa).
SPONSOR	Advanced Accelerator Applications International SA 4 rue de la tour de l'ile 1204 Geneva, Switzerland Tel: +41 (0)22 519 0700 www.adacap.com / info@adacap.com
IND NO.	135350
PROTOCOL NUMBER	A206D-A01-001 / NCT03490032
PROTOCOL VERSION/DATE	Version 2.2, 22 February, 2018

[redacted]	[redacted], MD Advanced Accelerator Applications International SA Tel: [redacted] E-mail: [redacted]
[redacted]	[redacted] Advanced Accelerator Applications USA Inc. Tel: [redacted] E mail: [redacted]
[redacted]	[redacted] Advanced Accelerator Applications USA Inc. Tel: [redacted] E-mail: [redacted]
SCIENTIFIC ADVISOR CHAIRS	[redacted], MD, PhD. [redacted] Tel: [redacted] E-mail: [redacted]
	[redacted] Tel: [redacted] E-mail: [redacted]
CONTACTS FOR SAFETY REPORTING	Advanced Accelerator Applications SA 20 rue Diesel 01630 Saint Genis Pouilly Tel: +33 4 50 99 30 70 www.adacap.com / info@adacap.com

GOOD CLINICAL PRACTICE AND CONFIDENTIALITY STATEMENT

This trial will be conducted in compliance with the protocol, the principles of Good Clinical Practice (GCP), and applicable regulatory requirements.

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SYNOPSIS

Version Date	Version 2.2, 22 February, 2018
Protocol Number	A206D-A01-001
Phase of Development	Safety and Tolerability Study (Phase 1/2)
IND Number	135350
Investigational Product	^{68}Ga-PSMA-R2
Protocol Titles	A Phase 1/2 open-label, multi-center, safety and tolerability study of a single dose of ^{68}Ga-PSMA-R2 in patients with biochemical relapse (BR) and metastatic prostate cancer (mPCa)
Short Title	PROfind
Number of Study Sites	Approximately 4 clinical sites in the US
Sponsor	Advanced Accelerator Applications International SA
Co-Principal Investigators	[redacted], MD, PhD [redacted] and [redacted]
Investigational Product	Kit for the preparation of ^{68}Ga-PSMA-R2 for injection
Objectives	**Primary objective:** To assess safety and tolerability of a single administration of 3 mega Becquerel (MBq)/kg, but not less than 150 MBq and not more than 250 MBq, of ^{68}Ga-PSMA-R2 **Secondary Objectives** • To assess the pharmacokinetics (PK), biodistribution, and dosimetry of ^{68}Ga-PSMA-R2. • To establish the optimal imaging method for determining location and burden of positive lesions on ^{68}Ga-PSMA-R2 positron emission tomography (PET) imaging in patients in comparison with lesions identified with conventional imaging scans (computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan), and to calculate the agreement of ^{68}Ga-PSMA-R2 PET with conventional anatomical/functional imaging on a per patient basis.
Endpoints	**Primary Endpoints:** • Adverse events (AEs) and serious adverse events (SAEs) • Absolute changes and changes from baseline in clinical laboratory parameters, vital signs, electrocardiogram (ECG) **Secondary Endpoints:** • Generation of decay corrected tissue time-activity curves (TACs) from ^{68}Ga-PSMA-R2 PET/CT images in normal organs and tumor lesions. • Urinary excretion of ^{68}Ga-PSMA-R2 • Calculation of half-life of ^{68}Ga-PSMA-R2 in blood

	• Generation of non-decay-corrected time activity curves from ^{68}Ga-PSMA-R2 PET/CT images in normal organs and tumor lesions • Calculation of residence times in organs and tumor lesions of ^{68}Ga-PSMA-R2 • Calculation of absorbed doses and effective whole-body dose of ^{68}Ga-PSMA-R2 • To establish optimal threshold, expressed as standard uptake value (SUV) to discriminate positive PET imaging results from negative ones. • Burden and location of tumor lesions detected by ^{68}Ga-PSMA-R2 in comparison with standard imaging modalities such as CT/MRI and/or bone scan and/or biopsy. • Calculation of patient level agreement of ^{68}Ga-PSMA-R2 PET imaging relative to conventional techniques in prostate cancer patients
Study Design	This study will consist of 2 parts. • During the first part (Phase 1), approximately 6 patients with biochemically recurrent PCa will receive the investigational product (IP) and will remain at the site for approximately 6 hours post-injection in order to assess the PK, biodistribution vs. time, and dosimetry for critical organs. Patients will receive a single dose of 3 MBq/kg, ($\geq$ 150 and $\leq$ 250 MBq), of ^{68}Ga-PSMA-R2 intravenously. Serial blood and urine samples will be collected for PK characterization and dosimetry and whole-body PET/CT will be acquired at selected time points (0-4 hours) to determine organ and tumor absorbed doses. Safety assessments will be conducted after IP administration on Day 1, and during follow-up on Days 7 and 28. • In the second part of the study (Phase 2), two groups of approximately 12 patients will be enrolled (patients with PCa in biochemical recurrence (PCa-BR), and patients with prostate cancer in the metastatic stage (mPCa)). Enrollment will be capped at 12 patients in each group to ensure an even distribution of patient conditions. If preliminary data analysis from the Phase 1 part of the study provides sufficient dosimetry data, all patients will undergo whole body PET/CT imaging optimized for time (up to 2 time points) according to the data analysis from the Phase 1 component of the study.
Study Population	Patients with histologically confirmed adenocarcinoma of prostate staged as PCa-BR or mPCa
Study Duration	Approximately 6 weeks: up to 2 weeks of screening assessment, a 1-Day IP administration and imaging period, and three safety follow-up visits, at least one hour after the administration, then 7 Days and 28 Days after the administration. End of the study is defined as the date the last patient enrolled completes the 28 Days safety follow-up.
Treatment Duration	One Day/single IP administration
Number of Patients Planned	Approximately 30 patients will be enrolled in this trial. Phase 1 will include approximately 6 patients with adenocarcinoma of prostate origin staged as PCa-BR. Phase 2 will be comprised of 2 groups: one of approximately 12 patients with PCa-BR and another of approximately 12 patients with mPCa.
Inclusion Criteria	1. Male patients, 18 years of age or older. 2. Signed and dated written informed consent by the patient prior to any study-specific procedures. 3. Histologically confirmed adenocarcinoma of the prostate. a. Biochemical recurrence: defined as prostate specific antigen (PSA) level of $\geq$ 0.2 ng/mL after radical prostatectomy or PSA nadir plus 2 ng/mL after radiation therapy with corresponding CT/MRI or bone scan revealing absence of local recurrence or metastatic lesions.

	OR b. Metastatic disease: defined as both, castration-sensitive or castration-resistant mPCa (presence of at least one metastatic lymph-node, visceral metastasis and/or bone metastasis). c. At least 2 weeks must have elapsed between last anti-cancer treatment administration and the administration of the imaging product, ^{68}Ga-PSMA-R2. 4. Prior major surgery must be at least 12 weeks prior to study entry. 5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2, with a life expectancy ≥ 6 months. 6. Adequate bone marrow reserve and organ function as demonstrated by complete blood count, and biochemistry in blood and urine at Screening: o Hemoglobin (Hb): > 8.0 g/dL o Platelet count of > 50.000/mm^3 7. Serum creatinine < 1.5 ´ upper limit normal (ULN) or estimated glomerular filtration rate (eGFR) > 50 mL/min based upon The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [34]. 8. For male patients with partners of childbearing potential, agreement to use barrier contraceptive method (condom) and to continue its use for 28 days after IP administration.
Exclusion Criteria	1. Pathological finding consistent with small cell, neuroendocrine carcinoma of the prostate or any other histologies different than adenocarcinoma. 2. Administered a radioisotope ≤ 10 physical half-lives prior to the day of PET/CT. 3. Current severe urinary incontinence, hydronephrosis, severe voiding dysfunction, or need of indwelling/condom catheters. 4. Uncontrolled pain or incompatibility that results in patient's lack of compliance with imaging procedures 5. Other known co-existing malignancies except non-melanoma skin or low grade superficial bladder cancer unless definitively treated and proven no evidence of recurrence for at least 5 years. 6. Patient with known incompatibility to CT scans. 7. Any evidence of severe or uncontrolled systemic or psychiatric diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including human immunodeficiency virus (HIV) and untreated hepatitis B, hepatitis C. Screening for chronic conditions is not required. 8. Patients who have received any investigational agent within the last 28 days are excluded from participation in this trial. 9. Any acute toxicity due to prior chemotherapy and/or radiotherapy that has not resolved according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. 10. Known allergy, hypersensitivity, or intolerance to the investigational product or its excipients. 11. Patient unlikely to comply with study procedures, restrictions and requirements and judged by the Investigator to be unsuitable for study participation.
Investigational Product, Dosage, and Mode of Administration	^{68}Ga-PSMA-R2 will be prepared on the day of the administration using a reaction vial containing a lyophilized labelling formulation of 30 µg of PSMA-R2 to be reconstituted with the addition of $^{68}GaCl_3$ solution coming from a GMP ^{68}Ge/^{68}Ga generator and reaction buffer. After 7 minutes at 95°C, the final labelled ^{68}Ga-PSMA-R2 product is ready for injection. The reconstituted product is stable for at least 4 hours after labelling.

	Before administration, quality control (QC) testing will be performed and the exact volume to be injected will be determined (based on the weight of the patient, the estimated time of injection, and the physical decay of the radionuclide). The final volume and activity of the reconstituted product provides enough solution for QC testing and for the subsequent administration.
Imaging	Dosimetry assessments will be conducted based on time activity curves (TAC), time integrated activity coefficients (TIAC), absorbed doses and effective dose. Maximum standardized uptake values (SUV_{max}) will be used to determine the tumor lesions, defined as focal areas of abnormal uptake showing a higher SUV_{max} than surrounding tissue. Identification of the time points post-injection with the highest observed number of lesions and the highest SUV_{max}, SUV_{mean} values and the tumor to background ratios for each SUV will be determined. The later will be conducted separately for each imaging time point (approximately at 20-30 minutes, 1, 2, 3-4 hours) post-injection. For Phase 2, all patients will undergo whole body PET/CT imaging optimized for time (up to 2 time points) according to the data analysis from the Phase 1 component of the study. Qualitative visual analysis of total number of lesions identified by PET, and semi-quantitative analysis by means of SUV_{max} and SUV_{mean} values per dose and time points will be conducted.
Distribution and Dosimetry	Dosimetry data will be issued from serial imaging data. Organ radiation absorbed doses will be calculated.
Blood and Urine Collection for PK and Dosimetry	Serial samples (blood and urine) will be collected from approximately 6 patients on Day 1 visit for PK, biodistribution and dosimetry analysis as outlined below. • Blood: Immediately prior to IP administration, approximately 5, 10, 20, 40 minutes, 1, 2, 4 and 6 hours post injection. • Urine: Pre-injection, approximately 0-20 minutes after IP administration, approximately 0-1 hour, 1-2 hours, 2-4 hours, 4-6 hours post-injection
Discontinuation from Study Treatment	Patients may withdraw from this study if: • It is in the patient's best interest as determined by the study Investigator • Withdrawal of consent • Any manifestation of unacceptable toxicity defined as any major adverse event (AE) related to treatment procedures • Lost to follow-up • Early study termination by the Sponsor
Safety and Tolerability	All patients will be evaluated for safety and tolerability based on results of vital signs recorded at each visit, ECG after IP administration on Day 1, and laboratory assessments (including hematology, blood chemistry, urinalysis) at each study visit. Adverse events will be recorded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Adverse events will be recorded and monitored from the time the patient signs the informed consent form (ICF) until 28 Days end of study visit. Serious adverse events (SAEs) will be submitted to the Advanced Accelerator Applications (AAA) pharmacovigilance department and will be followed until stabilization or resolution.
Sample Size Calculations	The number of patients in this study is not based on statistical power considerations. It is anticipated that data for up to 30 evaluable patients distributed in the two study phases will provide sufficient data to assess the safety and tolerability of the intravenous administration of ^{68}Ga-PSMA-R2.
Statistical Analysis	All statistical analyses will be primarily descriptive in nature and will include summaries and graphical presentations of the data. Data presentations will group the PCa-BC and mPCa populations and also include an overall total patients column.

	The safety assessments will be performed after a single administration of ^{68}Ga-PSMA-R2. Safety and tolerability will be primarily evaluated by the incidence of AEs, changes in clinical laboratory values (hematology, blood chemistry, and urinalysis), vital signs (temperature, blood pressure, heart rate, and respiratory rate), and ECGs. All adverse events will be listed on an individual basis. They will be summarized by System Organ Class and preferred term including relationship and severity on a patient basis. Clinical laboratory parameters, vital signs and ECG parameters will be summarized and presented graphically as observed values and changes from baseline at each measuring time. Clinical laboratory parameters will also be analyzed in terms of tabulations to within, below or above normal ranges provided by the laboratory of each site. Descriptive statistics and graphical presentation will be produced for bio-distribution, radiation dosimetry and PK data as appropriate. The number and location of lesions identified by ^{68}Ga-PSMA-R2 PET imaging will be summarized and compared with those identified with conventional imaging techniques. Tumor uptake will be evaluated by SUV. SUV_{mean} and SUV_{max} will be determined along with tumor to background ratio and these will be summarized descriptively. Positive and negative lesions by the two imaging techniques will be cross tabulated overall and by localization area on a lesion level and a patient level. Agreement calculations will be performed on a patient level and tests of association may be performed where appropriate. Preliminary explorations of ^{68}Ga-PSMA-R2 imaging performance relative to cytology and/or histopathology findings from archival and/or recent biopsy specimens will be performed for patients with biopsy data available.

STUDY PROCEDURES AND ASSESSMENTS

Table 1 Schedule of Procedures and Assessments

	Screening (Day -14 to Day -1 (+1 day)	Imaging Day 1 (+1 day)	Safety Follow-up Day 7 (+1 day)	Safety Follow-up Day 28 (+1 day)
Informed consent	X			
Inclusion/Exclusion Criteria Assessment	X			
Medical History & Demographics	X			
ECOG Performance Status	X	X	X	X
Standard 12-lead ECG	X	X[a]		
Disease Assessment: Imaging (CT/MRI or Bone Scan)	X[b]			
Vital Signs: Temperature (Temp), Blood Pressure (BP), Heart Rate (HR), and Respiratory Rate (RR) [c]	X	X	X	X
PSA	X			
Lab Analysis: Hematology, Blood Chemistry[d]	X	X	X	X
Urine Analysis (Dipstick)[e]	X	X	X	X
^{68}Ga-PSMA-R2 Administration		X		
^{68}Ga-PSMA-R2 PET/CT (Dosimetry)[f]		X		
PK and Dosimetry Sample Collection (Blood)[g]		X		
PK and Dosimetry Sample Collection (Urine)[h]		X		
Adverse Event Collection	X	X	X	X
Concomitant Medications	X	X	X	X

[a] On Day 1, 12-Lead ECG will be collected after dosage administration.

[b] All patients are required to undergo a CT/MRI and bone scan if indicated (can be performed ≤ 2 months prior to study entry).

[c] On Day 1 vital signs (temp, BP, HR, and RR) will be performed before and after to ^{68}Ga-PSMA-R2 injection and also at the end of ^{68}Ga-PSMA-R2 PET/CT scan.

[d] Peripheral venous blood samples will be collected at each visit. On Day 1, blood samples will be collected after administration of ^{68}Ga-PSMA-R2.

[e] A urine sample will be collected at each visit and analyzed at the clinical site if dipstick results are abnormal. Sample collection on Day 1 will be performed after the administration of IP

[f] Patients in Phase 1 only: PET/CT scans will be performed at approximately 20-30 min and at 1, 2, 3-4 hours post-injection. For patients in Phase 2 only, PET/CT scan will be performed at up to 2 optimal time points as determined in the Phase 1 portion of the study.

[g] Patients in Phase 1 only: PK and dosimetry blood samples will be collected immediately prior to injection, approximately 5, 10, 20, 40 minutes, 1, 2, 4, and 6 hours post injection.

[h] Patients in Phase 1 only: Urine sample for PK will be collected pre-injection, approximately 0-20 minutes after IP administration, and approximately 0-1 hours,1-2 hours, 2-4 hours, and 4-6 hours post-injection.

BP = blood pressure; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HR = heart rate; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; PSA = prostate specific antigen; PSMA = prostate specific membrane antigen

INVESTIGATOR'S STATEMENT

I agree to conduct the study as outlined in the protocol entitled "A Phase 1/2 open-label, multi-center, safety and tolerability study of a single dose of ^{68}Ga-PSMA-R2 in patients in biochemical relapse (BR) and metastatic prostate cancer (mPCa)." in accordance with the guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

1. The right for the Sponsor and the Regulatory Agencies to inspect study facilities and pertinent records any time they may consider appropriate and in a reasonable manner that ensures patient confidentiality. If this study is to be inspected by a Regulatory Agency, the Sponsor should be notified as soon as possible;
2. When required, submission of the proposed clinical investigation, including the protocol and the consent form to a duly constituted Institutional Review Board (IRB) or Ethics Committee (EC) for approval and acquisition of written approval for each, prior to the use of the experimental study drug;
3. Obtaining the written informed consent prior to administration of study drug or any protocol-specified procedures or intervention that involve risk, and that contains all the elements of consent as specified in any applicable regulation and has been previously approved by the Sponsor and the IRB/EC;
4. Submission of any proposed change in or deviation from the protocol to the IRB/EC using a signed formal amendment document approved by the Sponsor. Any proposed changes or amendment in the protocol require that the informed consent also reflect such changes or amendment and that the revised informed consent be approved by the IRB/EC;
5. Documentation and detailed explanation of individual protocol deviations on the appropriate case report form page or in letters to the Sponsor;
6. Reports of Serious Adverse Events (SAE) to the Sponsor or designee (e.g. CRO) within 24 hours by email/fax and a written report of the serious adverse event within 24 hours after the Investigator's initial receipt of the information;
7. After the 28-Day safety follow-up period, all SAEs possibly related to ^{68}Ga-PSMA-R2 or to the study procedures must be reported to the Sponsor
8. Documentation of SAEs, as outlined in the protocol, to the IRB/EC within 15 calendar Days of their disclosure and 7 Days for death and life threatening;
9. Submission of timely progress reports to the IRB/EC as determined by the IRB/EC, and/or Sponsor, at appropriate intervals or upon request if applicable;

Regulations require an Investigator to prepare and maintain adequate and accurate case histories designed to record all observations and other data (such as study drug accountability) pertinent to the investigation on each individual enrolled in the study. These records must be maintained by the Investigator for a period established in the current regulation in place or a period of time determined by the Sponsor following the date a marketing application is approved for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, until 2 years or a period of time determined by

the Sponsor after the investigation is discontinued and the appropriate regulatory authorities are notified.

In addition, I agree to provide all the information requested in the case report form in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing case report forms.

I also agree that all information provided to me by the Sponsor, including protocols, case report forms, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be disclosed in confidence with the IRB/EC overseeing the study conduct. I also understand that reports of information about the study or its progress will not be provided to anyone who is not involved in the study other than to the Principal Investigator, or in confidence to the IRB/EC or to the legally constituted regulatory authorities.

Principal Investigator(s):

Name: Signature:	Date:

Name: Signature	Date:

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: Safety and tolerability study of ^{68}Ga-PSMA-R2 in patients with prostate cancer (PCa).

PROTOCOL NUMBER: Protocol A206D-A01-001

Signatures on this page denote approval of the study protocol outline by the respective Sponsor Department

Role	Name and contact details	Signature and Date
[redacted]	[redacted], MD Advanced Accelerator Applications International SA 4 rue de la tour de l'ile 1204 Geneva, Switzerland Tel: [redacted] E mail: [redacted]	
[redacted]	[redacted], MD Advanced Accelerator Applications USA Inc. 350 Fifth Avenue, Suite 6902 New York, NY 10118, USA Tel: [redacted] E mail: [redacted]	
[redacted]	[redacted] Advanced Accelerator Applications USA Inc. 350 Fifth Avenue, Suite 6902 New York, NY 10118, USA Tel: [redacted] E mail: [redacted]	
[redacted]	[redacted], MSc Pharm Advanced Accelerator Applications SA 20 rue Diesel 01630 Saint Genis Pouilly, France Tel: [redacted] Mobile: [redacted] E-mail: [redacted]	

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AAA	Advanced Accelerator Applications
AE(s)	Adverse Event(s)
ALAT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ASAT	Aspartate Aminotransferase
BP	Blood Pressure
BR	Biochemical Relapse
BUN	Blood Urea Nitrogen
Cast(s)/lpf	Cast per low power field
CI	Confidence Interval
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Curriculum vitae
DOTA	1,4,7,10-Tetraazacyclododecane-N,N',N",N'''-tetraacetic acid
^{68}Ga	Gallium radioisotope 68
^{68}Ga-PSMA-R2	^{68}Ga-PSMA ligand
^{68}Ge	Germanium radioisotope 68
GGT	Gamma-Glutamyl Transpeptidase
EANM	European Association of Nuclear Medicine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEC	European Economic Community
EMA	European Medicines Agency
E.U.	Endotoxin Units
EU	European Union
EURATOM	European Atomic Energy Community
EuQPPV	European Qualified Person for Pharmacovigilance
GBq	Giga Becquerel
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practices
Hb	Hemoglobin
H	Hour

HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference of Harmonization
ID	Identification
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
I.V.	Intravenous
kVp	peak kilovoltage
LDH	Lactate Dehydrogenase
MBq	Mega Bequerel
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute(s)
mPCa	Metastatic Prostate Cancer
mCRPC	Metastatic Castration-resistant Prostate Cancer
MRI	Magnetic Resonance Imaging
PCa	Prostate Cancer
PCa-BR	Prostate Cancer in Biochemical Relapse
PET	Positron Emission Tomography
PI	Principal Investigator
PK	Pharmacokinetics
PRLT	Peptide Radio-Ligand Therapy
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Cell
ROI	Region Of Interest
RR	Respiratory Rate
SAE	Serious Adverse Events
SOC	System Organ Class
SOP	Standard Operation Procedures
SPECT	Single Photon Computed Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TAC	Time Activity Curves
TIAC	Time Integrated Activity Coefficient
TRUS	Trans Rectal Ultrasound
Temp	Temperature
ULN	Upper Limit Normal
VOI	Volume Of Interest

VCT	Volume Computed Tomography
WBC	White Blood Cell
WHO	World Health Organization
WMA	World Medical Association

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1. INTRODUCTION

Prostate cancer (PCa) is the second most common type of cancer in men worldwide leading to substantial morbidity and mortality [1]. It represents the second most common cause of cancer death in men in the USA and the third most common cause of death in developed countries [2-3].

Most cases of PCa are curable if diagnosed at an early stage. Nevertheless, a number of patients will progress to metastatic PCa or metastatic castration-resistant PCa (mCRPC). Despite the effectiveness of hormone therapy in the treatment of metastatic PCa, patients who live long enough will ultimately succumb to mCRPC.

Up to 40% of the patients with PCa develop biochemical recurrence within 10 years after initial local treatment with curative intent [4]. Usually an increase of the PSA-level precedes a clinically detectable recurrence by months to years [5]. However, it cannot differentiate between local, regional or systemic disease with the necessary precision that is essential for further disease management [6]. Morphological imaging methods exhibit considerable limitations: sensitivity ranges between 25% and 54% for the detection of local recurrence by trans rectal ultrasound (TRUS) or contrast-enhanced CT and is moderately improved by using functional MRI techniques [6-8]. The sensitivity for detection of lymph node metastases of CT or MRI is reported to be 30-80% [9]. Early detection of bone metastasis is also critical in the management of patients with high risk prostate cancer [10]. Currently available bone scan or CT scan imaging techniques rely on non-specific osteoblastic activity and mineralization changes, respectively, rather than detection of actual tumor cells.

1.1. Prostate Specific Membrane Antigen

Prostate Specific Membrane Antigen (PSMA) is a type II integral membrane glycoprotein identified on human prostatic carcinoma cell lines. The PSMA protein has a unique 3-part structure consisting in a 19-amino-acid internal portion, a 24-amino-acid transmembrane portion, and a 707-amino-acid external portion. The PSMA gene is located on the short arm of chromosome 11 in a region that is not commonly deleted in prostate cancer. PSMA triggers a signal that allows internalization of the protein on the cell surface into an endosomal compartment. This characteristic seems to be useful for diagnostic and therapeutic (theragnostic) approach in which PSMA could be used as an antigenic target or as a specific docking-station for tailored small molecules [11].

Increased PSMA expression has been detected most notably in prostate cancer; though, it was also detected in the peritumoral and endotumoral capillaries of a variety of malignancies including renal cell carcinomas, transitional cell carcinomas, and colon carcinomas [12]. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in most primary and metastatic lesions [13-14]. Immuno-histochemical studies have shown that PSMA expression increases in cases of de-differentiated, metastatic, or hormone-refractory disease [15] and its expression level is a significant prognosticator for disease outcome [16]. Since internalization occurs much easily after binding of small-molecule ligands to PSMA, these molecules may be the ideal candidates for peptide-radio-ligand therapy [17].

In addition to the promising emerging data on the use of PSMA-radioligands for the treatment of mPCa [18-20], PSMA is also expressed in normal tissues with relatively high density to potentially induce off-target effects, as in the red bone marrow, the salivary and lacrimal glands [21], or the kidneys [22]. The unwanted radio-ligand uptake can reach elevated absorbed doses in normal tissues [23-24] due to the variable tissue-binding site density and blood flow perfusion rate, which may lead to toxic effects.

For some forms of peptide-radio-ligand therapy, the assessment of tumor uptake by means of pre-therapeutic imaging is considered predictive of the therapeutic success if associated with high tumor-absorbed dose [25], where the SUV may serve as indicator [26-28]. For an appropriate patient selection, based on the specific expression of PSMA in the tumor, the correlation between pre-therapeutic SUV and the calculated absorbed tumor dose are considered critical. Image-based absorbed dose calculations are needed as a means to achieve the optimal therapeutic effect of therapy while minimizing the possibility of side effects.

The treatment of a localized PCa can vary considerably depending on several factors, options may include active surveillance, radical prostatectomy, or radiotherapy. Definitive treatment of PCa using prostatectomy or radiation therapy often results in cure. About 70% of patients who undergo definitive treatment with a radical prostatectomy remain biochemical progression-free at 10 years. External beam radiation therapy or brachytherapy, can also be utilized for definitive therapy with curative intent of clinically localized prostate cancer, with a 10-year biochemical progression-free survival of 50–70% [29]. Unfortunately, despite high cure rates after definitive therapy, approximately 30-35% of patients will still experience a biochemical progression within 10 years of initial treatment, and about one third of those will later develop radiographic evidence of disease progression [30]. At the time of biochemical recurrence, localization of disease is pivotal as it helps deciding the appropriate clinical management, which may include salvage therapy for local recurrence and/or systemic therapy for metastatic disease [31].

The positron emitter ^{68}Ga is gaining great interest in nuclear medicine because of its suitable physical characteristics such as the high positron yield (89%), and the short half-life (68 minutes). The clinical use of ^{68}Ga-labelled compounds hails from the 1960s, applying initially to central nervous system processes [32-33]. Despite the availability of ^{68}Ga for more than 30 years, recognition of its uses for clinical PET is relatively recent and only in the last decade is being applied to pre-clinical models of human disease and to clinical studies.

The ^{68}Ga-labeling procedures currently implemented in clinical practice vary among the clinical centers and involve a complex sequence of operations that are still largely based on the use of automatic synthesis modules. This is because the synthesis procedures are still not robust and standardized enough to avoid the processing of generator eluate and the purification of the final product before administration.

1.2. ^{68}Ga-PSMA-R2 (Investigational Product for PET Imaging)

The proposed investigational product (IP), a 2 vial- kit for the preparation of ^{68}Ga-PSMA-R2, allows a simple ^{68}Ga-labeling procedure based on direct reconstitution of a pre-formulated good manufacturing practices (GMP) kit with the eluate provided by commercially available GMP

^{68}Ge/^{68}Ga generators. This method does not require any processing of the eluate or any additional filtration or purification step.

In support of its potential use for the diagnosis of PCa in biochemical recurrence and metastatic disease, a Phase 1/2 study with a novel diagnostic radio-labelled PSMA-ligand is proposed. The purpose of this study is to assess the safety and tolerability, and to evaluate the preliminary diagnostic value of ^{68}Ga-PSMA-R2 in patients with PCa in biochemical relapse, and a comparison to conventional morphological imaging for cancer lesions in patients with mPCa.

1.3. Study Rationale

PSMA is an ideal target to develop radiopharmaceuticals for peptide radio-ligand therapy (PRLT) based on small molecule PSMA inhibitors. Studies based on PET and SPECT imaging using ^{68}Ga, ^{18}F, ^{123}I, and ^{99m}Tc labeled small molecule glutamate urea heterodimers have clearly documented the specific localization of these agents in PCa lesions of the prostate gland, and in the distant metastatic lesions.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To evaluate the safety and tolerability of 3 MBq/Kg, but not less than 150 MBq and no more than 250 MBq, of a single i.v. administration of ^{68}Ga-PSMA-R2.

2.1.2. Secondary Objectives

- To assess PK, biodistribution, and dosimetry of ^{68}Ga-PSMA-R2.
- To establish the optimal imaging method for determining location and burden of positive lesions on ^{68}Ga-PSMA-R2 PET imaging in comparison with lesions identified with conventional anatomical imaging scans (CT/MRI and bone scan), and to calculate the agreement of ^{68}Ga-PSMA-R2 PET with conventional anatomical imaging on a per patient basis.

2.2. Endpoints

2.2.1. Primary Endpoints

- Incidence and severity of AEs, and SAEs
- Absolute changes and changes from baseline in clinical laboratory parameters (hematology, blood chemistry and urine values), including assessment of shifts from baseline to abnormal values
- Absolute changes and changes from baseline in vital signs & ECG parameters

2.2.2. Secondary Endpoints

- Generation of decay corrected TACs from ^{68}Ga-PSMA-R2 PET/CT images in normal organs and tumor lesions.
- Urinary excretion of ^{68}Ga-PSMA-R2
- Calculation of half-life of ^{68}Ga-PSMA-R2 in blood
- Generation of non-decay-corrected time activity curves from ^{68}Ga-PSMA-R2 PET/CT images in normal organs and tumor lesions
- Calculation of residence times in organs and tumor lesions of ^{68}Ga-PSMA-R2
- Calculation of absorbed doses and effective whole-body dose of ^{68}Ga-PSMA-R2
- To establish optimal threshold, expressed as SUV to discriminate positive PET imaging results from negative ones.
- Burden and location of tumor lesions detected by ^{68}Ga-PSMA-R2 in comparison with standard imaging modalities such as CT/MRI and/or bone scan and/or biopsy.
- Calculation of patient level agreement of ^{68}Ga-PSMA-R2 PET imaging in prostate cancer patients

3. STUDY DESIGN AND PATIENT POPULATION

3.1. Study Design

This is an open label, multi-center, single dose, Phase 1/2 study to evaluate the safety and tolerability of 3 MBq/Kg, but not less than 150 and no more than 250 MBq, of ^{68}Ga-PSMA-R2 in adult patients with PCa expressing PSMA receptors.

This study will consist of 2 phases.

Phase 1:

During the Phase 1 portion of the study, approximately 6 patients with biochemically recurrent PCa will receive the IP and will remain at the site for approximately 6 hours post-injection in order to assess PK, biodistribution, and dosimetry for critical organs. Patients will receive a single dose of 3 MBq/kg, ($\geq$ 150 MBq and $\leq$ 250 MBq), of ^{68}Ga-PSMA-R2. The product will be prepared prior to administration and injected intravenously and each patient will undergo a whole-body PET/CT scan following IP administration. Serial blood and urine samples will be collected for PK characterization and dosimetry. Safety assessments will be conducted after IP administration on Day 1, and during follow-up on Days 7 and 28.

Dosimetry will be assessed in 6 patients, they will undergo static whole-body PET/CT images at 0-4 hours to determine absorbed doses by the normal organs and target tumor lesions.

Phase 2:

Two groups of approximately 12 patients will be enrolled in the Phase 2 portion of the study (patients with PCa-BR, and mPCa). Enrollment will be capped at 12 patients in each group to ensure an even distribution of patient condition. If preliminary data analysis from the Phase 1 portion of the study provides sufficient dosimetry data, all patients will undergo whole body PET/CT imaging optimized for time according to the data analysis from the Phase 1 component of the study.

Patients who have signed the informed consent and are eligible for study participation according to the inclusion and exclusion criteria will receive a single intravenous bolus of ^{68}Ga-PSMA-R2 on Day 1.

This study is comprised of 4 clinical visits and will be conducted in 3 study periods including: Screening, administration/ imaging, and safety follow-up period (final/early termination).

4. STUDY POPULATION

Up to 30 evaluable patients with histologically confirmed PCa (staged as PCa-BR or mPCa) will be enrolled.

4.1. Inclusion Criteria

1. Males, 18 years or older
2. Signed and dated written informed consent by the patient prior to any study-specific procedures.
3. Histologically confirmed adenocarcinoma of the prostate.
   a. biochemical recurrence: defined as PSA is ≥ 0.2 ng/mL after radical prostatectomy or PSA nadir plus 2 ng/mL after radiation therapy with corresponding CT/MRI or bone scan revealing absence of local recurrence or metastatic lesions.

      OR

   b. metastatic disease: defined as both, castration-sensitive or castration-resistant mPCa (presence of at least one metastatic lymph-node, visceral metastasis and/or bone metastasis).
   c. At least 2 weeks must have elapsed between last anti-cancer treatment administration and the administration of the imaging product, ^{68}Ga-PSMA-R2.
4. Prior major surgery must be at least 12 weeks prior to study entry.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-2, with a life expectancy ≥ 6 months.
6. Adequate bone marrow reserve and organ function as demonstrated by complete blood count, and biochemistry in blood and urine at Screening:
   - Hemoglobin (Hb): >8.0g/dL

- Platelet count of > 50.000/mm^3

7. Serum creatinine < 1.5 ´ upper limit normal (ULN) or estimated glomerular filtration rate (eGFR) > 50 mL/min based upon The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
8. For male patients with partners of childbearing potential, agreement to use barrier contraceptive method (condom) and to continue its use for 28 days after IP administration.

4.2. Exclusion Criteria

1. Pathological finding consistent with small cell, neuroendocrine carcinoma of the prostate or any other histologies different than adenocarcinoma.
2. Administered a radioisotope ≤ 10 physical half-lives prior to the day of PET/CT.
3. Current severe urinary incontinence, hydronephrosis, severe voiding dysfunction, or need of indwelling/condom catheters.
4. Uncontrolled pain or incompatibility that results in patient's lack of compliance with imaging procedures
5. Other known co-existing malignancies except non-melanoma skin or low grade superficial bladder cancer unless definitively treated and proven no evidence of recurrence for 5 years.
6. Patient with known incompatibility to CT scans.
7. Any evidence of severe or uncontrolled systemic or psychiatric diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol, or active infection including human immunodeficiency virus (HIV) and untreated hepatitis B, hepatitis C. Screening for chronic conditions is not required.
8. Patients who have received any investigational agent within the last 28 days are excluded from participation in this trial.
9. Any acute toxicity due to prior chemotherapy and/or radiotherapy that has not resolved according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Section 11.2).
10. Known allergy, hypersensitivity, or intolerance to the investigational product or its excipients.
11. Patient unlikely to comply with study procedures, restrictions and requirements and judged by the Investigator to be unsuitable for study participation.

4.3. Screen Failures

A "screen failure" is a patient who consented to participate but was not eligible to participate in the study.

For patients not considered eligible after the screening period, the reason for not being eligible must be documented. No additional assessments are needed.

4.4. End-of-Study

End of study will be achieved by a patient after all study procedures and the follow up visit are completed and no further study related activities are required, or when a patient withdraws consent at any time.

Study will be terminated when all patients have completed their end of study activities or at any time due to sponsor decision.

5. STUDY MEDICATION

5.1. Investigational Product for PSMA Imaging: ^{68}Ga-PSMA-R2

The full name of the Investigational Product (IP) is "^{68}Ga-PSMA-R2 kit for radiopharmaceutical preparation".

The IP is a sterile 2-vial kit which consists of:

- Vial 1: PSMA-R2, 30 µg, powder for solution for injection, to be reconstituted with a solution of gallium-68 chloride ($^{68}GaCl_3$) in HCl eluted from a GMP ^{68}Ge/^{68}Ga generator;
- Vial 2: Reaction buffer. Vial 2 is to be added to the reconstituted Vial 1.

The kit has to be used in combination with a solution of ^{68}Ga in HCl provided by a GMP ^{68}Ge/^{68}Ga generator to obtain ^{68}Ga- PSMA-R2 solution for injection, being the radiolabeled imaging product, which can be directly injected to the patient.

After reconstitution with the eluate from a GMP ^{68}Ge/^{68}Ga generator and addition of kit reaction buffer (vial 2), the reconstituted solution must be used within 4 hours.

The volume of ^{68}Ga- PSMA-R2 solution for injection, corresponding to the radioactive dose to be administered, is calculated according to the estimated time of injection, on the basis of the current activity provided by the generator and of physical decay of the radionuclide (half-life, 68 minutes).

This is a mono-dose product.

Vial 1 is a powder for solution for injection containing PSMA-R2 as active ingredient. The powder is packed in 10 mL Ultra-inert Type I Plus glass vials. Vial 2 Reaction buffer contains no active ingredient. Reaction buffer solution is contained in a 10-mL cyclic olefin polymer vial

The kit will be prepared, packaged and released according to Sponsor Standard Operating Procedures (SOPs), GMP guidelines, International conference on harmonization (ICH) GCP guidelines, and applicable local laws/regulations.

5.2. Investigational Product Packaging, Labeling, and Handling

The investigational product will be supplied by the Sponsor as a sterile, two-vial kit for reconstitution with ^{68}Ga solution eluted from approved commercial GMP ^{68}Ge/^{68}Ga generator.

Labeling will be handled per the Sponsor's SOP. The site personnel will maintain shipping, dispensing, and collection logs provided in Investigator file by the Sponsor or designee (e.g. CRO). The IP will be inventoried according to the protocol instructions and applicable regulations and will be stored in a secure, locked place with limited authorized access at the investigational site.

After reconstitution with ^{68}Ga solution eluted from approved commercial GMP ^{68}Ge/^{68}Ga generator, the investigational product is a radioactive substance, and it must be handled and administered by qualified/authorized personnel only, and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations.

5.3. Investigational Product Administration and Accountability

When investigational product is received at the site, the Investigator, Pharmacist or authorized designee shall check for accurate delivery and acknowledge receipt by signing and dating the shipping documentation, and returning the reception form to the Sponsor or designee. A copy of this documentation shall be retained for the Investigator file.

Any use or manipulation of the IP shall be carefully recorded on the IP accountability form provided by the Sponsor, and an accurate accounting must be available for verification by the clinical research associate (CRA) at each monitoring visit.

IP accountability records shall include:

- confirmation of the IP delivery to the study site;
- inventory at the study site;
- use of IP by each patient; and
- it should include delivery dates, quantities, lot/batch numbers and manufacture/expiration dates for the IP. Investigators should maintain records to document adequately that:
    - the patients were administered the doses specified by the protocol and any amendment(s); and
    - all IP provided by the Sponsor were fully reconciled.

Unused investigational product must be destroyed per local practice.

The administration volume (containing the planned dose) is determined according to the estimated time of injection, on the basis of the physical decay of the radionuclide (half-life, 68 minutes).

5.4. Patient Release and Radioprotection Precautions

Following administration of ^{68}Ga-PSMA-R2, patients should remain at the clinical site for an additional 6 hours in an area with suitable radiation shielding to protect others from unnecessary exposure. At the time of release, patients are given written instructions which outline the precautions the patient must take to minimize radiation exposure to people around them.

Excessive release of hormones or bioactive substances are not expected to occur following treatment, therefore, observation of patients by overnight hospitalization is not required.

5.5. Concomitant Medications

Previous and concomitant medications will be coded using World Health Organization (WHO) dictionary. Type and incidence of previous and concomitant medications will be tabulated (generic terms).

All medications taken at the start of Screening until the end of the study, or early termination, are to be recorded. This includes prescription and over-the-counter medications taken during this time frame.

5.6. Prohibited Concomitant Medications and Procedures

While participating in this study cancer targeted therapy including but not limited to chemotherapy, hormonal therapy (except for LHRH or GnRH), or external beam radiation is not permitted within four weeks prior to ^{68}Ga-PSMA-R2 PET/CT scan.

Any medications which are considered necessary for the patient's welfare, may be given at the discretion of the Investigator; however, if it belongs to the list above the patient will have to be withdrawn from the study treatment.

6. STUDY PROCEDURES AND ASSESSMENTS

A schedule for all procedures and evaluations to be conducted in this study is outlined in the visits schedule presented in

of this protocol.

6.1. Informed Consent

Each potentially eligible patient will be informed of the study objectives and overall requirements. Before conducting any of the screening tests, the Investigator or an authorized delegate will explain the study fully to the patient using the patient information leaflet/ICF. If the patient is willing to participate in the study, written informed consent will be requested after the patient has been given sufficient time to consider participation and the opportunity to ask for further details. The ICF will be signed and personally dated by both the patient and the Investigator or an authorized delegate. A copy of the signed consent form will be provided to the patient, and the original will be retained with the source documents.

A screening log will be completed for all patients who sign the ICF. These patients will be identified with their identification (ID) number; in addition, eventual reasons for exclusion from the study will be recorded.

6.2. Screening Visit (Day -14 to Day -1)

Each patient will be allocated a unique patient ID number, which will identify the patient throughout the study.

During the Screening visit, the following activities will be performed:

- Written informed consent will be obtained prior to performing any study related activities
- Inclusion/exclusion criteria will be checked.
- Each patient's demography: date of birth, gender, ethnicity, weight, height, medical history, and relevant baseline characteristics will be recorded.
- Historic and current prostate cancer related biopsies (prostate and metastatic sites) should be performed per local practice. All data related to date of biopsy, site of lesion, and pathology results will be collected in the database.
- ECOG performance status must be assessed (Section 11.1). The medical history will be recorded as well as all concomitant medications taken including therapies for PCa.
- All patients will have undergone histological/immunohistochemical exam at the time of the original PCa diagnosis and CT/MRI exam, within two months before enrollment.
- Vital signs will be assessed.
- ECG (12-lead) will be recorded.
- Blood samples for PSA, hematology, blood chemistry and urinalysis will be obtained.
- All concomitant medications including PCa therapies taken 2 weeks prior to the IP administration date through the end of study will be recorded.
- Any AEs occurring after the ICF signature will be recorded and followed until resolution.

6.3. Administration/ Imaging Period (Day 1)

Eligible patients who have met all inclusion criteria and none of the exclusion criteria will receive an injection of 3 MBq/Kg, but not less than 150 MBq and no more than 250 MBq of ^{68}Ga-PSMA-R2. Patient will enter the trial unit on the morning of the exam. Each subject will be allocated one single imaging kit.

- All concomitant medications including PCa therapies taken 2 weeks prior to the IP administration date through the end of study will be recorded.
- Any AEs occurring after the ICF signature will be recorded and followed until resolution.
- Vital signs will be assessed before and after the ^{68}Ga-PSMA-R2 injection and at the end of the PET/CT exam.
- ECOG performance status will be assessed.
- Patient will be injected intravenously one single bolus dose of ^{68}Ga-PSMA-R2.
- ECG (12-lead) will be recorded immediately after IP administration.

- For patients entering in Phase 1: PET/CT scans will be performed at approximately 20-30 minutes and at 1, 2, 3-4 hours post-injection.
- Patients in the Phase 1 portion of the study will undergo distribution/ dosimetry analysis
- For patients entering Phase 2, patients will have PET/CT imaging reduced to up to 2 whole body scans within the optimal time frame, to confirm the high tumor to background ratio, and agreement compared to standard conventional method.
- Samples for hematology, biochemistry and urinalysis will be collected after the administration of IP.
- Patients entering Phase 1 only: PK and dosimetry blood samples will be collected immediately prior to IP administration, approximately 5, 10, 20, 40 minutes, as well as immediately after, 1, 2, 4, and 6 hours post IP administration.
- Patients entering Phase 1 only: Urine sample for PK will be collected Pre-injection, approximately 0-20 minutes after IP administration , 0-1 hour, 1-2 hours, 2-4 hours, 4-6 hours post-injection.

6.4. Safety Follow-up Visits (Day 7 ± 2 Days and Day 28 ± 3 Days)

After IP administration, two safety follow-up visits will be performed on Day 7 (± 2 Days) and Day 28 (± 3 Days).

- All concomitant medications including PCa therapies taken 2 weeks prior to IP administration date through the end of study will be recorded.
- Any AEs occurring after the ICF signature will be recorded and followed until resolution.
- ECOG performance status is assessed.
- Vital signs will be assessed.
- Blood samples for hematology, biochemistry and urinalysis will be obtained.

6.5. Special Study Assessments

6.5.1. Histological / Immunohistochemical Assessment

All patients are required to have histological confirmation of adenocarcinoma of the prostate based on surgery/biopsy specimens of the primary tumor or the metastatic disease. Most recent biopsy sample collected should be used. All data related to date of biopsy, site of lesion, and pathology results will be collected in the database. No new biopsy is required for the purposes of this study.

6.5.2. CT/MRI/Bone Scan

All patients are required to undergo a CT/MRI within 2 months prior to enrollment. If a CT is performed, this should be a standard diagnostic thoracic and abdominopelvic CT scan, with a slice thickness of ≤ 5 mm; if MRI is performed, the injection of a contrast medium is recommended. Standard imaging modality for patients with PCa in biochemical relapse or with

metastatic disease, as applicable, will be performed as per routine institutional practice. Per RECIST v1.1 the imaging modality must be consistent throughout the study. Tumor assessment imaging procedures will be performed per local practice. CT scan is the preferred method and MRI will be done per local standard-of-care. Patients with either previous history of metastatic disease to the bone or any symptoms indicative of metastatic bone disease will require a bone scan.

All patients with metastatic prostate cancer enrolled in Phase 2 portion of the study will have their imaging procedures assessed locally for clinical management and centrally for comparison with ^{68}Ga-PSMA-R2 PET imaging.

6.5.3. Clinical Laboratory Assessments

Clinical laboratory assessments for safety monitoring will be performed by an accredited local laboratory. Blood and urine samples for hematology, serum chemistry and urinalysis, will be prepared using standard procedures.

PSA sample will be collected at Screening (unless performed within one month of enrollment and results are available), and results will be entered into the eCRF.

The following laboratory tests will be performed at Screening, Day 1 (after the administration of the IP), Day 7, and Day 28:

- Hematology: White blood cell (WBC) count with differential, red blood cell (RBC) count, Hb, hematocrit, platelet count, mean corpuscular volume (MCV).
- Blood chemistry profile: albumin, alkaline phosphatase (AP), alanine transaminase (ALAT), aspartate transaminase (ASAT), blood urea nitrogen (BUN), corrected calcium, chloride, creatinine, eGFR (preferably CKD-EPI), glucose, uric acid, gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), potassium, sodium, total bilirubin and total protein.
- Urinalysis: (dipstick), appearance, color, pH, specific gravity, protein, glucose and occult blood, RBC and WBC counts, Casts per low power field (Casts/lpf), Protein (dipstick test accepted).

Table 2 summarizes general laboratory assessments to be performed.

Table 2 Summary of Laboratory Assessments

Hematology	Blood Chemistry	Urinalysis*
• WBC with differential	• BUN	• Appearance
• RBC	• Serum creatinine	• Color
• Platelets	• eGFR	• pH
• Hb	• Albumin	• Specific gravity
• MCV	• Total bilirubin	• Glucose
• Hematocrit	• AP	• Occult blood
• PSA (Screening visit only)	• AST/ASAT	• RBC/hpf
	• ALT/ALAT	• WBC/hpf
	• Gamma-GT	• Casts/lpf
	• Sodium	• Protein (dipstick test accepted)
	• Potassium	
	• Chloride	
	• LDH	
	• Corrected Calcium	
	• Glucose	
	• Total protein	
	• Uric acid	

*A urine sample will be collected at each visit and analyzed at the clinical site if dipstick results are abnormal.
WBC = white blood cell; RBC = red blood cell; Hb = hemoglobin; MCV = mean corpuscular volume; PSA = prostate specific antigen; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; AST/ASAT = aspartate aminotransferase; ALT/ALAT = alanine aminotransferase; gamma-GT = gamma glutamyl transferase; LDH = lactate dehydrogenase; pH = potential of hydrogen; hpf = high power field; lpf = low power field.

The total volume of blood required per patient for clinical laboratory assessment will be approximately 70 mL (approximately 15 mL on each sampling at Screening, Day 7, and Day 28), and approximately 25 mL on Day 1. Blood and urine samples will be analyzed in an accredited local laboratory.

6.5.4. Imaging assessments

6.5.4.1. Imaging Procedure During the Phase 1 Portion of the Study

^{68}Ga-PSMA-R2 PET/CT imaging (four scans) will be performed using a standard integrated PET/CT system. Patients will be placed on the scanner table to allow a vertex to mid-thigh low-dose CT scan without contrast (used for anatomic localization and attenuation correction), followed immediately by emission scan after ^{68}Ga-PSMA-R2 injection. PET scans will be performed from vertex to mid-thigh in 3D (3-dimentional acquisition) mode. Please refer to Section 6.5.4.2 for more details.

Maximum standardized uptake values (SUV_{max}) will be used to determine the tumor lesions, defined as focal areas of abnormal uptake showing a higher SUV_{max} than surrounding tissue.

Identification of the time points post-injection with the highest observed number of lesions and the highest $SUV_{max,}$ SUV_{mean} values and the tumor to background ratios for each SUV will be determined. The later will be conducted separately for each imaging time point (20-30 minutes, 1, 2, 3-4 h) post-injection through qualitative visual analysis of total number of lesions identified by PET, and semi-quantitative analysis by means of SUV_{max} and SUV_{mean} values and time point will be conducted.

Lesions suggestive of PCa will be counted and analyzed for radioactive uptake (expressed as SUV_{mean} and SUV_{max}) and localization. Any PCa lesion will be counted and analyzed. Tumor contrast will be measured by dividing the SUV_{mean} of tumor lesions by the SUV_{mean} of the background (e.g. gluteal musculature) and by dividing the SUV_{max} of tumor lesions by the SUV_{mean} of the background.

6.5.4.2. Biodistribution and Dosimetry Phase 1 Portion of the Study

Patients enrolled in the biodistribution and dosimetry set will undergo for a series of static whole-body PET/CT images at 20-30 minutes and at 1, 2 and 3-4h to determine absorbed doses to normal organs and to target tumor lesions. A low dose non-contrast-enhanced CT will be performed at 20-30 minutes, 1, 2, and 3-4 hours post injection. Immediately after CT scanning, PET scan will be performed from vertex to mid thighs in 3D (3-dimensional acquisition) mode at 20-30 minutes, 1, 2, and 3-4 hours imaging. The emission data will be corrected for dead-time, scatter, and decay, and resulting voxels were stored in units of Bq/mL. Reconstruction will be conducted with an ordered subset expectation maximization algorithm. Attenuation correction will be performed using low-dose non-enhanced CT data acquired at each time point.

Regions of Interest (ROIs)/ volume of interests (VOIs) will be drawn on the static whole-body PET images over the critical organs and tumor lesions to generate time-activity curves, and assess the time integrated activity coefficients (TIAC) (35). Up to 10 lesions which have the highest tumor to background ratio will be selected for dosimetry analysis for each patient.

Dosimetry calculations will be issued from the analyses of organs receiving the highest dose, identified visually. ROIs/VOIs will be placed over these organs to determine relative radiotracer uptake calculated as a percentage of the activity (%IA).

Tissue activity curves will be generated and fitted to mono- and bi-exponential curves to yield TIAC values. To assess pharmacokinetics and red marrow dosimetry, serial venous blood sampling withdrawn at immediately prior to IP administration, 5, 10, 20, 40 minutes, as well as immediately after, 1, 2, 4 and 6 hours post IP administration will be analyzed. Urine samples pre-injection, approximately 0-20 minutes after IP administration, 0 to 1 hour, 1 to 2 hours, 2 to 4 hours, and 4 to 6 hours post-injection will be collected to complete biodistribution and dosimetry assessments. The absorbed doses (µGy/MBq) for critical organs will be evaluated, as well as the effective dose (µSv/MBq).

6.5.4.3. Whole Body PET/CT Imaging for Phase 2 Portion of the Study

Preliminary data analysis from the Phase 1 portion of the study will provide sufficient dosimetry data, therefore all Phase 2 patients will have PET/CT imaging reduced to up to 2 whole body

scans within the optimal time frame, to confirm the high tumor to background ratio, and agreement compared to standard conventional method.

^{68}Ga PSMA-R2 PET/CT imaging will be performed using a standard integrated PET/CT system. Patients will be placed on the scanner table to allow a vertex to mid-thigh low-dose CT scan without contrast (used for anatomic localization and attenuation correction), followed immediately by emission imaging after ^{68}Ga-PSMA-R2 injection. A non-contrast-enhanced CT will be performed using routine investigational site imaging parameters. Immediately after CT scanning, PET scan will be performed from vertex to mid thighs in 3D (3-dimensional acquisition) mode. The scan duration will be 3 min for each bed position. The emission data will be corrected for dead-time, scatter, and decay, and resulting voxels were stored in units of Bq/mL. Attenuation correction will be performed using low-dose non-enhanced CT data acquired at each time point.

6.5.5. Other Safety Assessments

Results of the ECGs, and vital sign assessment will be evaluated by the Investigator for evidence of immediate safety concerns or for changes in values that indicate a potential danger for the patient to continue in the study. The Investigator should contact the medical monitor from Sponsor or designee (e.g. CRO) with questions regarding vital sign values.

6.5.5.1. Standard 12-Lead ECG

ECGs will be recorded at the screening visit and at Day 1 (after the administration of the IP) to measure the different ECG intervals (RR, PR, QRS, and a more extended QT evaluation according to ICH E14, and heart rate, HR). A single ECG will be taken supine, after 5 minutes rest, and not immediately after a meal. The parameters will be measured as a mean value of minimally 3 beats. The Investigator will note in the electronic CRF (eCRF) whether the ECG is normal or abnormal, as well as the clinical relevance of abnormal ECGs. Clinically relevant abnormalities will be recorded on the AE page of the eCRF.

6.5.6. Concomitant Medications and Other Restrictions

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the case report form, including any changes that have occurred during the study.

6.6. Reasons for Withdrawal

A patient may withdraw from the study at any time for any reason (see section 6.7).

The Investigator may discontinue the patient from the study if he experiences a serious or intolerable adverse event(s) or discontinue from study if the patient is in violation of the protocol.

Protocol can be terminated by the sponsor prematurely.

If a patient is discontinued due to an AE, the event will be followed until it is resolved.

6.7. Handling of Withdrawals

When a patient withdraws from the study, the reason(s) for withdrawal must be recorded by the Investigator in the patient's source document and the relevant page of the eCRF. For patients who remain in the study but fail to return for final assessments, every effort should be made to collect the information specified in the protocol.

It is vital to obtain follow-up data for any patient withdrawn as consequence of an AE. Every patient who discontinues prematurely must be contacted 15 Days (± 3 Days) after discontinuation to obtain adverse event information.

6.8. Sponsor's Termination of Study

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons. In that event, the Sponsor will immediately notify and instruct investigational sites, who in turn must promptly notify their patients and respective Institutional Review Board / Ethics Committee (IRB/EC) and or regulatory authorities.

6.9. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

6.9.1. Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

6.9.2. Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

6.10. Replacement Policy

Patients who discontinued for any reason during the study will not be replaced.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Adverse Events and Serious Adverse Events

The safety of the radiolabeled imaging final product ^{68}Ga-PSMA-R2 will be assessed through recording, reporting and analyzing medical conditions, infections, vital signs (temperature, blood pressure, heart rate, and respiratory rate), ECGs, and safety laboratory tests (blood chemistry, hematology, urinalysis).

Adverse events encountered from the time of ICF signature through the follow-up period (until Day 28 after administration of ^{68}Ga-PSMA-R2) will be recorded by the Investigator on the appropriate AE pages of the eCRF as defined in the following sections. Adverse events will be recorded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Section 11.2).

Only adverse events with start date on or after the IP administration date will be considered treatment emergent.

After the follow-up period, the Investigator must report to the Sponsor only SAEs possibly related to ^{68}Ga-PSMA-R2 or to the study procedures (see SAE definition in Section 7.6.3).

7.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an investigational product, regardless of causal relationship and even if no investigational product has been administered.

In this study, the term “investigational product” refers to the radiolabeled imaging final product ^{68}Ga-PSMA-R2.

Unchanged/stable pre-existing, chronic medical conditions present at baseline, or those medical conditions related to the underlying disease should not be recorded on AE pages of the eCRF. However, in case of worsening of a pre-existing condition, this should be considered and reported as AEs.

- Relationship to IP,
  - based on temporal association: temporal relationship between administration of the IP and AEs occurrence is compatible,
  - based on AEs presentation and IP characteristics
  - If no alternative explanations (patient’s medical history, patient’s concomitant treatment, circumstance of AEs occurrence) are identified

- Not related to IP:
    - In case an alternative explanation regarding the AEs occurrence had been identified.

7.2. Abnormal Laboratory Findings and Other Objective Measurements

All clinically relevant abnormal laboratory findings must be captured and reported as AEs. Abnormal laboratory findings and other objective measurements that meet the criteria for SAE, result in discontinuation of the Investigational Product, or require medical intervention, should be captured and reported on the SAE/AE pages of the eCRF.

If reporting an abnormal laboratory finding on the AE pages of the eCRF, a clinical description or diagnosis should be recorded rather than the abnormal value itself, if this is available (for example “anemia” rather than “decreased red blood cell count” or “hemoglobin = 10.5 g/dL”).

In the event of unexplained clinically abnormal laboratory values, the tests should be repeated immediately and followed up until returns to normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, this must be recorded on the eCRF.

7.3. Baseline Medical Conditions

Medical conditions present at the screening visit, that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not adverse events. These medical conditions should be adequately documented on the appropriate page of the eCRF, i.e. medical history page.

However, worsening of medical conditions present at the initial study visit, either severity or frequency during the study should be recorded and reported as AEs.

7.4. Baseline Medications

Any medication taken prior to investigational product administration will be considered baseline medications. Any medications taken from the Day of administration (Day 1) to the end of the trial will be considered concomitant medications and captured on the appropriate eCRF page.

7.5. Clinical Condition Impairment

Exacerbation or worsening of symptoms will be recorded on the AE page of the eCRF.

7.6. Procedures for Obtaining, Recording and Reporting Adverse Events

7.6.1. Obtaining Adverse Events

Adverse event data will be obtained by the Investigator at scheduled study visits, based on information spontaneously provided by the patient and/or through questioning. The patient will be instructed upon signing the ICF to contact the Investigator if any adverse or unusual event occurs during his participation in the study.

To obtain adverse events, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. For example:

- How did you feel since your last visit?
- Have you had any health problems since you were visited?

In the case that a patient was seen by a different health care professional (e.g. at a different institution), in relation with an adverse event, every effort should be made by the Investigator to contact the treating physician in a timely manner to obtain all necessary information and report the event appropriately in the eCRF.

7.6.2. Recording of Adverse Events in the eCRF

Adverse events will be recorded in the patient's medical records (source document) and eCRF, whether observed by the Investigator, the investigational staff, or spontaneously reported by the patient.

As quality and precision of acquired AE data is of key importance, Investigators should use the adverse event definitions provided in the sections above and observe the following guidelines when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (e.g. 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical descriptions or diagnosis rather than component signs or symptoms (e.g. 'congestive heart failure' rather than 'dyspnea, rales and cyanosis'). However, signs and symptoms that are considered unrelated to an identified disease or syndrome might be reported as individual AEs on the eCRF if no clearer diagnosis can be drawn.
- Adverse events occurring secondary to other events (e.g. sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record on AE pages of the eCRF.

It is important that each AE report includes a description of the event, seriousness status and criteria, duration, severity, and causality, other causality factors (if any), any concomitant medications dispensed, concomitant procedure prescribed or other action taken, including dose modification and/or discontinuation of the investigational product and its outcome as per the end of the reporting period.

7.6.3. Serious Adverse Events Requiring Expedited Reporting

Any SAE requires expedited reporting to the Sponsor or designee, regardless of relationship to the Investigational Product.

An SAE is defined as an AE that at any dose:

- **Resulted in death**: i.e. the AE causes or contributes to the death.

- **Was life threatening**: i.e. the AE places the patient at immediate risk of death; the definition does not apply to an AE that hypothetically might cause death if it was more severe.
- **Required or prolonged hospitalization**: i.e. the AE requires at least a 24-hour in-patient hospitalization or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before trial entry, for social reasons or for normal disease management (including treatment adjustment) are not to be considered as SAE according to this criterion.
- **Is a congenital anomaly or birth defect**: i.e. an adverse outcome in a child or fetus of a patient's partner exposed to the investigational product, before conception or during pregnancy.
- **Resulted in persistent or significant disability or incapacity**: i.e. the AE resulted in a substantial disruption of the patient's ability to conduct normal life functions.
- **Was a medically important condition**: Such an event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the above definition should also usually be considered as serious.

Investigators must indicate the possible cause(s) of the SAE in the appropriate section of the SAE reporting form (e.g. underlying disease, study treatment, other treatment[s], study procedures, or other cause[s]).

7.6.4. Pregnancy

The occurrence of a pregnancy of a partner of a trial patient discovered within 1 week after last administration of the IP and up to the end of follow-up period, is to be communicated to the Sponsor in an expedited manner with the same procedure and timelines as for SAEs (see paragraph 7.6.5), independently from the occurrence of an AE.

7.6.5. Expedited Reporting Procedure

Besides AEs and SAEs entry in the eCRF, investigators must notify the Sponsor or designee **within 24 hours** of awareness of a new SAE/pregnancy case or of new information on a previously reported SAE/pregnancy case (follow-up), regardless of relationship to the investigational product.

The Investigator/Reporter must complete an SAE form and the following minimum information is required as initial notification:

- Clear identification of the Investigator/Reporter with full contact information,
- A unique clinical trial identification
- Patient identification details (trial number, site number, identification code number, date of birth),
- Investigational Product administration details (product name, dose and dates),

- Reported event as a diagnosis term with its description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available)
- Date of onset of the event,
- Reason(s) for considering the event serious,
- Investigator causality assessment

The opinion of the Investigator about the causal relationship between the event and the IP is required. Even if not all the facts are known, an initial report should be sent to the Sponsor.

The initial report must be followed by a detailed report as soon as possible.

Any additional information received on an initial SAE report must be sent to the Sponsor following the same timelines.

If considered necessary by the Sponsor and in order to allow a sound medical assessment of the reported SAEs, the Sponsor may request additional documentation such as technical investigation reports, histology findings, hospital discharge documents. All these additional documents must be blinded with respect to the patient's name and provided to the Sponsor in due time by email (pharmacovigilance@adacap.com).

When the Investigator determines that no additional information is likely to be available, a final report should be provided.

7.6.6. Reporting to the Competent Authorities and IRB/IEC

The Sponsor or designee will assume responsibility for appropriate reporting of Suspected Unexpected Serious Adverse Reaction (SUSAR) to the Competent Authorities and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB) according to local laws and regulations.

The Sponsor will inform Competent Authorities, IRB/IEC, and Investigators of "findings that could adversely affect the safety of patient and impact the conduct of the study or alter the IRB/IEC's approval/favorable opinion to continue the study".

Copies of safety reports should be kept in the Investigator file as well as inserted into the relevant Investigator Brochure. In addition, all correspondence relating to their notification to the Competent Authorities and IRB/IEC should be maintained in the Investigator file.

Development safety update report (DSUR)/IND report will be sent to inform competent authorities, IRB/IEC, and Investigators.

7.7. Reporting Period

Adverse Events are collected on an ongoing basis from signing of Informed Consent until the last follow up visit.

All SAEs, including deaths, independently of causality, that occur from informed consent until the last scheduled follow-up visit will be recorded on an SAE form, in addition to the eCRF data entry. After the last follow-up visit, the Investigator must report to the Sponsor only SAEs possibly related to ^{68}Ga-PSMA-R2 or to the study procedures.

All SAEs must be followed-up by the Investigator until resolution or stabilization, and follow-up information must be reported to the Sponsor according to the reporting procedure.

All pregnancy cases occurring one week after IP administration and until the last follow-up (Day 28) will be reported according to the SAE reporting procedures. All pregnancy reports will be followed-up until delivery.

A last batch of queries will be sent after Last Patient Last Visit for all AEs with ongoing/unknown outcomes. After the last batch of queries with all collected data have been fully processed, eCRFs and database will no longer be updated. Only SAEs and medically relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization. Beyond this defined reporting period, any new unsolicited serious AE spontaneously reported to CRO/Sponsor by the Investigator would however be collected and processed by pharmacovigilance.

Any patient who received a partial or full dose of the investigational product and who withdraws prematurely or is withdrawn by the Investigator from the trial, should have a follow-up safety visit 28 (± 3) Days after the investigational product administration.

If a patient is documented as lost-to follow-up or consent withdrawal, ongoing/unknown outcome AEs will not be followed-up.

For screen failure patients, new AEs and updates must be recorded in eCRFs until the date the patient was determined to be a screen failure. Beyond that date, only SAEs possibly related to the investigational product or to the study procedures will be reported to the CRO/Sponsor.

8. STATISTICAL METHODS AND ANALYSIS

8.1. Sample Size Calculation

The primary objective of the trial is to assess the safety and tolerability of ^{68}Ga-PSMA-R2. Data for this objective will be reported descriptively. No formal statistical sample size calculation was done. The planned sample size includes a total of up to 30 patients which is believed to provide sufficient data to assess the safety and tolerability of ^{68}Ga-PSMA-R2, and to reliably estimate distribution and dosimetry parameters. In addition, an overall sample size of 30 patients should provide reasonable precision around estimations of preliminary targeting properties of the ^{68}Ga-PSMA-R2 imaging. For example, if patient level agreement of 83.3% if observed (for e.g. if 25 patients had lesions detected by ^{68}Ga-PSMA-R2 imaging out of 30 patients in the trial), then the 95% CI around this would be 66.4% to 92.7%.

8.2. Analysis Methods

Statistical analysis will be described in detail in the statistical analysis plan prior to database lock.

Due to the single arm design of the study, the primary focus of the statistical analysis will be on descriptive statistics and graphical presentations of data. Continuous variables will be presented as number of non-missing values, mean, standard deviation, median, minimum, maximum and quartiles. For categorical variables, descriptive statistics will include counts and percentages per category. Confidence intervals will be computed when appropriate, usually as 95% intervals, but 80% intervals may also be produced in some instances due to the early phase nature of this trial. Continuous variables will be compared where relevant using the most appropriate test such as paired analysis Mann-Whitney-Wilcoxon U test. Proportions will be compared using the appropriate test among Fisher's exact test or McNemar test. Pearson's or Spearman linear regression analysis will be used to explore potential relationships between two continuous variables as appropriate. Any hypothesis testing that is performed will be interpreted as exploratory and no emphasis will be placed on nominal significance levels. No adjustment for multiplicity will be applied and missing data will not be replaced.

Data presentations will group the PCa-BC and mPCa populations and also include an overall total column.

For analysis purposes, baseline for a given assessment will be defined as the last non-missing value prior to the administration of ^{68}Ga-PSMA-R2.

The Full Analysis Set will consist of all patients who enter the study and receive at least one dose of ^{68}Ga-PSMA-R2. The safety set in this case is identical to the full analysis set and so will not be de-fined as a separate set. The Per Protocol set consists of all patients in the full analysis set who complete the study according to the protocol with no major protocol violations. All analyses will primarily be performed on the full analysis set, select analyses may be repeated on the per protocol set if there are sufficient violations to warrant it and deviation of results by using the per protocol set will be discussed.

8.2.1. Safety and Tolerability Analyses

Safety evaluations on the full analysis set will be based on the incidence, type, severity and consequences (e.g. study discontinuation) of an AE as well as on clinically significant changes in the patient's ECGs, vital signs, and clinical laboratory results. ECG parameters will include heart rate (HR), RR interval, PR interval, QRS width and QTc interval. Statistical analysis includes descriptive tabulation using measures which are absolute and relative frequencies for categorical data and means, standard deviations, medians and interquartile ranges for continuous data for observed values as well as for changes from baseline in continuous parameters at each measuring time. Clinical laboratory data, ECGs and vital signs will also be presented graphically in terms of box plots of absolute values over time and changes from baseline over time. Clinical laboratory data will be summarized with respect to the normal ranges of values provided by the laboratory and with respect to pre-defined levels of change in these values.

All original AE/SAE terms will be coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version. All Adverse events will be listed on an individual basis. AEs will be summarized by System organ classes and preferred terms on a patient basis. Patients with more than one adverse event within a particular SOC and PT will be counted only once for that SOC and PT. The type and incidence of AEs/SAEs, as well as severity and causality will be tabulated on a patient basis using the worst severity/causality for patients with several AES within the same particular SOC and PT.

Only treatment emergent events will be included in summaries of AEs, but all adverse events will be presented in listings. Summaries of adverse drug reactions will also be produced, which are defined as treatment emergent adverse events at least possibly related to treatment.

8.2.2. Analysis of Biodistribution, Pharmacokinetic and Dosimetry Data

The analysis of biodistribution, pharmacokinetic and dosimetry endpoints will consist of descriptive summaries and graphical presentations of the derived parameters on the sub-population of the full analysis set who underwent dosimetry assessments. The ^{68}Ga-PSMA-R2 biodistribution, and absorbed dose in critical organs will be determined and stability will be analyzed using HPLC measurements. Regions of interest (ROI) for critical organs and tumor lesions will be drawn using the acquired images resulting in time-activity curves with quantitative fractions of administered activity. Dosimetry calculations will be issued from the analyses of organs receiving the highest dose, identified visually. ROI will be placed over these organs to determine relative radiotracer up-take calculated as a percentage of the injected dose. Time activity curves (TACs) will be fitted to mono- and bi-exponential curves to yield cumulative activities. Urine samples approximately 0-2 hours and 4 hours post-injection will be collected to complete dosimetry and biodistribution assessments. The absorbed dose (µGy/MBq) for critical organs will be evaluated, as well as the effective dose (µSv/MBq). The effective dose represents a radiation protection quantity that provides an estimation of detriment to the whole organism. According to the National Institutes of Health, for effective doses under 3 mSv, the risk is considered to be "minimal". Effective radiation dose will be summarized descriptively as related and to the equivalent number of days of exposure to natural background.

8.2.3. Preliminary Targeting Properties of ^{68}Ga-PSMA-R2 PET Imaging

The number and location of lesions identified by ^{68}Ga-PSMA-R2 PET imaging will be summarized and compared with those identified with conventional imaging techniques. Tumor uptake will be evaluated by SUV. SUV_{mean} and SUV_{max} will be determined along with tumor to background ratio and these will be summarized descriptively. Positive and negative lesions by the two imaging techniques will be cross tabulated overall and by localization area on a lesion level and a patient level. Agreement calculations for ^{68}Ga-PSMA-R2 imaging relative to conventional techniques will be performed on a patient level and summarized descriptively. Tests of association may be performed where appropriate.

Preliminary explorations of ^{68}Ga-PSMA-R2 imaging results relative to cytology and/or histopathology findings from archival and/or recent biopsy specimens will be performed for patients with biopsy data available.

8.3. Data Management

8.3.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs or CD-ROM.

It is the responsibility of the Investigator to maintain adequate and accurate Case Record Forms (according to the technology used Paper or Electronic) to record all observations and other data pertinent to the clinical investigation.

The computerized handling of the data may generate additional requests to which the investigator is obliged to respond by confirming or modifying the data questioned. Should a correction be made, an audit trail will allow identification and tracking of the modification.

8.4. Monitoring, Auditing and Inspection

The study monitor and/or designee (e.g. contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with International Conference on Harmonisation (ICH) guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of investigational product dispensing, compliance, and accountability. A copy of the IP dispensing log must be provided to the sponsor upon request.

Before trial initiation, the Investigator will be informed of the anticipated frequency of monitoring visits. The Investigator will also receive notification before each monitoring visit during the course of the trial. It is expected that the Investigator and/or co-investigator(s) and other appropriate staff will be available on the Day of each visit in case questions arise.

The trial site may be audited either by the Sponsor or designee. The Investigator will be informed in advance of such an audit. The trial site may also be inspected by a regulatory agency, possibly more than once.

8.5. Monitoring Case Report Forms

The Investigator shall be responsible for the accuracy of the data entered on the eCRFs and medically validated for any SAE. All entries must be written in English. All deletions, additions or changes will be recorded and tracked (i.e. owner, date, original entry, etc.), including additional information if needed. The relevant pages of each eCRF must be fully completed within 5 working Days of the patient's visit to allow the CRAs to review and verify the forms promptly. Sufficient resources must be available to facilitate prompt eCRF completion and

collection. Request for data clarifications (queries) must be addressed within 5 working Days of receipt.

The Investigator will grant the Sponsor or designee, IRB/IEC, and regulatory bodies, direct access to the source documents to verify the data reported in the eCRFs and data queries (source documents are the originals documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial). Source documents should be available to support all the data recorded in the eCRF.

8.6. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution. In all instances, the confidentiality of the data must be respected.

9. Operational, Ethical, and Administrative Considerations

9.1. Data Quality Control

9.1.1. Documentation Required Prior to Initiation

The following documents will be required from the Investigator before the Initiation Visit:

- current signed and dated curricula vitae (CV) and license of the Investigator and any sub-Investigators and site personnel directly involved in the trial;
- normal ranges for all laboratory tests to be performed at the investigational site and a recent certification or accreditation of established quality control (or other documentation of established quality control or external quality assessment or other validation) and CV of the laboratory director;

- approved final protocol and informed consent;
- signed originals of the trial protocol and any amendments;
- completed and signed financial disclosure forms;
- signed originals of the clinical trial letter of agreement with the Sponsor; and
- local Regulatory Authorities' forms where required and/or delegation of authority log (Delegation of Responsibilities Form).

The Sponsor undertakes the obligation to obtain all the necessary approval from the competent regulatory authority prior to initiation of the trial.

9.1.2. Documentation Required During the Trial

The following will be required of the Investigator during the trial:

- current signed and dated curricula vitae and license of the Principal Investigator and Sub-investigators or site personnel who are delegated protocol-related responsibilities after trial initiation;
- documentation supporting any changes to clinical site staff, laboratory, and site locations;
- financial disclosure forms for any new staff directly involved in the trial;
- updates of normal ranges for all laboratory tests to be performed at the trial site and updates in certification or accreditation of established quality control (or other documentation of established quality control or external quality assessment or other validation);
- signed originals of any protocol amendments and signature pages;
- copies of any approvals from or other correspondence with the IRB/IEC; and
- updated Local Regulatory Authorities' forms and/or lists of delegated responsibilities.

9.1.3. Assignment of Patient Numbers and Dose allocation

A unique patient identification number will be assigned at the start of the screening period to each patient who signs the informed consent form. This number will identify the patient throughout the study. Patient identification number will include the protocol code 206D, a 4-digit country/site code, and a 3-digit patient number (ex: [redacted] for the first patient to be recruited).

Imaging kits will be allocated for single patient use.

9.1.4. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient

9.2. Ethical and Regulatory Considerations

9.2.1. Study Conduct

This study will be conducted according to the principles of the ICH E6 Guideline on GCPs and the principles of the World Medical Association (WMA) Declaration of Helsinki and its most recent amendment WMA General Assembly, Seoul, October 2008. The Investigator will conduct all aspects of this study in accordance with all national, state and local laws of the pertinent regulatory authorities.

Patient Selection: Up to 30 evaluable patients (for safety: patients who have received the study medication; for imaging: patients that have completed the imaging protocol) will be enrolled at up to 4 study sites. All patients will receive study imaging product only if they meet all the inclusion criteria and none of the exclusion criteria.

9.2.2. Informed Consent

A properly executed, written informed consent shall be obtained from each patient prior to entering the trial or performing any study-related procedure that involves a risk to the patient. A copy of the informed consent document to be used will be submitted by the Investigator to the IRB/IEC for review and approval prior to the start of the trial. The Investigator shall provide a copy of the signed informed consent to the patient, and the original shall be maintained in the patient's medical record. Additional elements of informed consent, if appropriate, must be provided to the patient. The patient must have signed and been given a copy of the informed consent document.

9.2.3. Confidentiality

All information provided to the Investigator by the Sponsor or designee including pre-clinical data, protocols, case report forms, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the trial. It is recognized that this information may be provided in confidence to the IRB/IEC. In addition, no report or information about the trial or its progress will be provided to anyone not involved in the trial other than to the Sponsor or designee, regulatory authorities and IRB/IEC; except if required by law. The Investigator must ensure that the patients' anonymity is maintained. In the eCRFs or other documents submitted to the Sponsor/CRO, patients should not be identified by their names, but by their assigned patient ID numbers and initials.

The Investigator must maintain a separate log (Master Patient List) of patients' codes, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor/CRO, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

9.2.4. Institutional Review Board/ Independent Ethics Committee Approval

Before initiation of the trial, the Investigator will submit the following to an IRB or IEC for approval:

- trial protocol and any amendments,
- patient information leaflets/ICFs and any other written materials to be provided to the patients,
- investigator brochure,
- details of any compensation to the patients, if applicable, and
- any other requested documents.

Copies of the approval and of all other correspondence with the IRB/IEC will be sent to the Sponsor or designee. The letter of approval must be dated, and the protocol number and the date of the protocol or amendment that was reviewed and approved must be specified. Likewise, the version and date of the patient information leaflet/ICF that was reviewed and approved must be specified.

A dated membership list of the voting members of the IRB/IEC who were present when the protocol was reviewed and approved, including their titles or occupations and their institutional affiliations, must be provided to the Sponsor or designee, before trial initiation.

The Investigator will submit a study report at least annually to the IRB/IEC that approved the protocol to comply with ICH GCP.

The Investigator will make all attempts to ensure that the IRB/IEC is constituted and operates in accordance with ICH GCP and with relevant local regulations.

9.3. Administration

9.3.1. Trial Record Retention

The Investigator will retain copies of all the essential documents (as defined by ICH GCP) for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements (for example, European Economic Community (EEC) Directive 91/507 requires retention of patient codes for at least 15 years after the completion or discontinuation of a trial, and retention of hospital records and other source data for the maximum time permitted by the institution where the trial takes place). The Investigator should take measures to prevent accidental or premature destruction of these documents.

The essential documents include:

- signed protocol,

- copies of the completed eCRFs,
- signed Informed Consent Forms from all patients who consented,
- hospital records and other source documents,
- IRB/IEC approvals,
- drug accountability records and trial correspondence.

The Investigator will inform the Sponsor or designee of the storage location of these essential documents, and must contact the Sponsor or designee before disposing of any of these documents.

The Sponsor or designee will inform the Investigator in writing when these documents no longer need to be retained.

9.3.2. Protocol Deviations and Amendments

The sponsor will not implement a change in the design or operation of the protocol or ICF without an IRB-approved amendment. Local amendments are highly discouraged unless strictly necessary due to regulatory purposes.

In the event of any medical emergency, the Investigator is free to perform any medical intervention or procedure deemed appropriate. Such events and procedures must be reported promptly to the Sponsor or designee.

9.3.3. Clinical Data Reporting

Sponsor or designee Notification: The Investigator will provide the Sponsor or designee with all completed patient case report form materials, adverse event reports, and evaluations of patient laboratory parameters.

Clinical Study Report: The Sponsor or designee will prepare a final report of the trial results after receiving, reviewing, and verifying the clinical data of the trial from the investigational site. For a multi-center trial, copies of this report may be supplied to each Investigator upon request.

Publication/Presentations: Any publication derived from this study's data will need to follow the publication charter which will be set up and agreed upon by the study co-chairs and the sponsor. The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. The results of the Phase 1 portion of the study may be published prior to the completion of Phase 2. Publication of study findings will be led by sponsor. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations.

9.3.4. Emergency Sponsor Contact

In emergency situations, the Investigator should contact the Sponsor or designee by telephone at the number listed on the title page of the protocol. Details of the methodology for identifying and reporting all AEs are in the Adverse Events Section (Section 7) of the protocol.

9.4. Financing and Insurance

9.4.1. Financial Disclosure

In accordance with the ICH E6 GCP Guideline, Part 54 Financial Disclosure by Clinical Investigators, addresses the laws requiring financial disclosure by clinical investigators involved in (directly or indirectly) the course of a clinical trial diagnostics, reads, and/or interpretations of clinical data or results. The Sponsor is required to obtain either:

- certification of the absence of certain financial interests or arrangements of clinical Investigators, or
- disclosure of certain financial interests or arrangements of clinical Investigators.

The Sponsor will request a statement attesting to any such financial arrangements.

Disclosure is required for those financial interests other than those entered under the Clinical Trial Agreement (CTA) for this trial.

9.4.2. Insurance

The sponsor has covered this study by means of insurance for the patient according to national requirements. The name and the address of the relevant insurance company, the certificate of insurance, the policy number, and the sum insured are provided in the Investigator's File.

10. REFERENCES

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11. APPENDICES

11.1. ECOG Performance Status

ECOG Performance Status*

Grade	ECOG
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

* As published in Am. J. Clin. Oncol.:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Revised: July 27, 2006

11.2. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Tables extracted from the FDA's September 2007 *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* are included below for reference. The full text of the guidance is available at the following URL:

https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.