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STATISTICAL ANALYSIS PLAN

A206D-A01-001

A PHASE I/II 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)

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V2.0, 29JUN2020

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 29JUN2020) for Protocol A206D-A01-001.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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2.0	29JUN2020	[redacted]	• Section 6.1 - The PCa-BR population group will be presented separately for Phase I and Phase II patients. • Section 15.2 – details of data presentations updated.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate aminotransferase
BLQ	Below the Lower Limit of Quantification
BUN	Blood Urea Nitrogen
CS	Clinically Significant
CT	Computed Tomography
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EG	Enterprise Guide
eGFR	Estimated Glomerular Filtration Rate
ENR	All Patients Enrolled
FAS	Full Analysis Set
^{68}Ga	Gallium radioisotope 68
^{68}Ga-PSMA-R2	^{68}Ga-PSMA ligand
g-GT	Gamma-glutamyl transpeptidase
Hb	Hemoglobin
LDH	Lactic acid dehydrogenase
MBq	Megabecquerel
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mPCa	Metastatic Stage Prostate Cancer
MRI	Magnetic Resonance Imaging
NCS	Not Clinically Significant
ODS	Output Delivery System
PCa	Prostate Cancer
PCa-BR	Biochemical Recurrence Prostate Cancer
PET	Positron Emission Tomography
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
PR	PR interval of the electrocardiogram; time duration between the P and R waves
PSA	Prostate specific antigen

PSMA	Prostate Specific Membrane Antigen
PT	Preferred Term
QRS	QRS interval of the electrocardiogram; duration of the QRS complex
QT	QT interval of ECG, duration between the Q and T waves
QTcB	QT interval of ECG corrected for heart rate using Bazett's formula
QTcF	QT interval of ECG corrected for heart rate using Fridericia's formula
Q1	First Quartile
Q3	Third Quartile
RBC	Red blood cell
RR	Time duration between two consecutive R waves of the electrocardiogram
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULQ	Upper Limit of Quantification
WBC	White blood cell
WHO-DD	Who Drug Dictionary

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety data, for Protocol A206D-A01-001. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 2.2, dated 22 February 2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is 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.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To assess the pharmacokinetics (PK) of ^{68}Ga-PSMA-R2.
- To assess 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.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is an open label, multi-center, single dose, Phase I/II 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 parts.

- During the first part (Phase I), approximately 6 patients with biochemically recurrent PCa will receive the investigational product (IP) and will remain at the site for approximately 6 hours post-administration in order to assess the PK, biodistribution vs. time, and dosimetry for critical organs. Patients will receive a single dose of 3 MBq kg. (≥ 150 and ≤ 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 II), 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 I part of the study provides sufficient dosimetry data, all patients will undergo whole body PET/CT imaging optimized for time (up to 2 timepoints) according to the data analysis from the Phase I component of the study.

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).

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section "STUDY PROCEDURES AND ASSESSMENTS" of the protocol.

4. PLANNED ANALYSES

The following analysis will be performed for this study:

- Phase I Analysis assessing PK, Biodistribution, Dosimetry and Imaging
- Final Analysis (combining Phase I and Phase II data)

This document will provide details for Phase I Biodistribution, Dosimetry and Imaging Analysis and Final Analysis. All planned analyses identified in this SAP will be performed by [redacted] Biostatistics following Database Lock.

4.1. PK ANALYSIS

Phase I PK Analysis will be described in a separate SAP written by the PK specialist from a third-party clinical pharmacokinetics vendor.

Derivation of the PK parameters and the PK summary tables, listings and figures, will be the responsibility of third-party clinical pharmacokinetics vendor.

4.2. BIODISTRIBUTION, DOSIMETRY AND IMAGING ANALYSIS

The biodistribution, dosimetry and imaging analysis will be split in two:

- The analysis using data from the principal scientist from a third-party radiation dosimetry vendor will be performed only for Phase I.
- The analysis using data from a third-party medical imaging vendor will be performed for both Phase I and

Phase II.

Summary tables, listings and figures needed for the biodistribution, dosimetry and imaging are described in section 15.

4.3. FINAL ANALYSIS

The final analysis will be conducted at the end of the study and will include the analyses of safety endpoints. This analysis will be based on the full analysis set (FAS) and may be repeated on the per protocol set (PPS).

5. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the final database lock. PK analysis set will be described in the SAP written by a third party clinical pharmacokinetics vendor.

5.1. ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled (ENR) set will contain all patients who provide informed consent for this study.

5.2. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all patients who receive at least one dose of study medication. The safety set in this case is identical to the full analysis set and so will not be defined as a separate set.

5.3. PER PROTOCOL SET [PPS]

The per-protocol set (PPS) will contain all patients in the FAS who complete the study according to the protocol with no critical or major protocol deviations. The decisions regarding critical and major protocol deviations, and the definition of the analysis population, will be finalized prior to database lock.

6. GENERAL CONSIDERATIONS

6.1. POPULATION SUMMARIZATION

In general, data will be presented by population.

- The following populations will be used in the analyses:

- PCa-BR
- mPCa

- The PCa-BR population group will also be presented separately for Phase I and Phase II patients.

6.2. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first and single administration of study medication, (Day 1 is the day of the first and single dose of study medication).

If the date of the event is on or after the reference date, then:

- Study Day = (date of event – reference date) + 1.

If the date of the event is prior to the reference date, then:

- Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear missing in the listings.

6.3. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date and time coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented.

Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/worst case value where required (e.g. shift tables).

Treatment Early termination data will not be included in by-visit summaries.

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.6. STATISTICAL TESTS

There will be no formal statistical testing of data.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

For quantitative measurements, percentage of change from baseline will be calculated as:

$$\left(\frac{\text{Test Value at Visit X} - \text{Baseline Value}}{\text{Baseline Value}}\right) \text{X } 100$$

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

There will be no statistical testing for safety data, and no covariate adjustment.

7.2. MULTICENTER STUDIES

The study will be conducted at approximately 4 sites in the US. All data will be pooled for summaries of safety with no summaries presented by center.

7.3. MISSING DATA

Missing safety data will not be imputed.

Missing severity and relatedness of AEs will be handled as described in sections 14.1.1.1 and 14.1.1.2 of this analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by [redacted] Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

The counts of the analysis sets will be presented:

- All Patients Enrolled Set (ENR)
- Full Analysis Set (FAS)
- Per Protocol Set (PPS)

The following patient disposition and withdrawals will be presented for the ENR set:

- Screened
- Screen failures
- Phase I
- Phase II

- Number of patients receiving study medication
- Completed study imaging assessments (assessed at Day 1)
- Discontinued from study, reason for premature discontinuation from study

Duration of follow-up will be presented for the ENR set. Duration of follow-up (day) is defined as date of completion/discontinuation - date of first administration + 1.

Critical and major protocol deviations (as defined in section 5.3) will be presented for the ENR set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS and PPS.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic characteristics will be reported:

- Age (years)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight (kg)
- Height (cm)

The following baseline characteristics will be reported:

- ECOG performance status at baseline (0, ≥1)
- PSA test (ng/mL)

11. MEDICAL AND PROSTATE CANCER HISTORY

Medical and prostate cancer history information will be presented for the FAS and PPS and will be coded using MedDRA version 21.0 or higher.

All reported medical and prostate cancer history will be listed.

11.1. MEDICAL HISTORY

Medical history will be presented by System Organ Class (SOC) and (Preferred Term (PT).

They will be sorted by decreasing frequency for SOC and for PT within SOC, based on total count.

See APPENDIX 2 for handling of partial dates for medical history.

11.2. PROSTATE CANCER HISTORY

The following prostate cancer history information, as reported in the eCRF, will be summarized:

- Time since first prostate cancer diagnosis (months)
- Time since first metastasis (months)
- Time since disease progression (months)
- Number of PSMA positive patients
- Number of patients by initial diagnostic stage (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, unknown)
- Number of patients by current diagnostic stage (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV, unknown)
- Number of patients by castration type (surgery, pharmacological, not applicable)
- Number of patients by primary and secondary Gleason score:
    - Primary Gleason score=3 and Secondary Gleason score=3
    - Primary Gleason score=3 and Secondary Gleason score=4
    - Primary Gleason score=4 and Secondary Gleason score=3
    - Primary Gleason score=4 and Secondary Gleason score=4
    - Primary Gleason score=4 and Secondary Gleason score=5
    - Primary Gleason score=5 and Secondary Gleason score=4
    - Primary Gleason score=5 and Secondary Gleason score=5
- Number of patients by Total Gleason score >=6 (6, 7, 8, 9, 10)

11.2.1. DERIVATIONS

- Time since first prostate cancer diagnosis (months) = (date of screening – date of first prostate cancer diagnosis + 1) / 30.4375
- Time since first metastasis (months) = (date of screening - date of first metastasis + 1)/ 30.4375
- Time since disease progression (months) = (date of screening – date of disease progression + 1)/ 30.4375

See APPENDIX 2 for handling of partial dates for prostate cancer history.

12. CANCER THERAPIES, MEDICATIONS, PROCEDURES AND RADIOTHERAPY

12.1. PRIOR AND CONCOMITANT CANCER THERAPIES

Prior and concomitant cancer therapies, as reported in the "Prior and Concomitant Cancer Therapy Medications" eCRF page, will be presented for the FAS and PPS using WHO-DD Preferred Names.

- Prior cancer therapies are those which started prior to the day of first and single dose of study medication.
- Concomitant cancer therapies are those which:
  - started prior to, on or after the first and single dose of study medication, AND
  - ended on or after the date of first and single dose of study medication or were ongoing at the end of the study.

Number of patients with at least one Line of therapy (Neoadjuvant, Adjuvant, Therapeutic for Metastatic Disease, Unknown), number of patients with at least one Therapy type (Chemotherapy, Hormonal, Biological, Immunotherapy, Other), number of patients with at least one Treatment intent (Curative, Palliative, Diagnostic, Salvage, Other) will be presented as well as the medication and the best response of the latest therapy the patient received (Complete response, partial response, stable disease, progressive disease, not evaluable).

12.2. PRIOR AND CONCOMITANT NON-CANCER MEDICATIONS

Medications will be presented for the FAS and PPS and coded using WHO Drug Dictionary version MAR2018 or higher if available at the time of the Database Lock. The medications will be summarized by WHO-DD Preferred Names, sorted by decreasing frequency based on total count.

See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

- Prior medications are those which started prior to the day of first and single dose of study medication.
- Concomitant medications are those which:
  - started prior to, on or after the first and single dose of study medication,
    AND
  - ended on or after the date of first and single dose of study medication or were ongoing at the end of the study.

All prior and concomitant prohibited/restricted medications outlined in protocol section 5.6, as determined by the medical advisor, will be listed.

12.3. PRIOR AND CONCOMITANT PROCEDURES

Prior and Concomitant Procedures (procedure, surgery or non-drug therapy) will be presented by SOC and PT. They will be sorted by decreasing frequency for SOC and for PT within SOC based on total count.
See APPENDIX 2 for handling of partial dates for prior and concomitant procedures. In the case where it will not be possible to define a procedure as previous or active/concomitant.

- Prior procedures are defined as those which started prior to the first and single dose of study medication.
- Concomitant procedures are defined as those which:
  - started prior to the first and single dose of study medication and are ongoing or active at the date of the first and single dose of study medication
    OR
  - started on or after the first and single dose of study medication.

12.4. PRIOR AND CONCOMITANT RADIOTHERAPY

Prior and concomitant radiotherapy, using radiation type as reported in the eCRF, will be presented by radiation type and treatment intent. The total dose received (Gray) will also be summarized.
See APPENDIX 2 for handling of partial dates for prior and concomitant radiotherapies. In the case where it will not be possible to define a radiotherapy as previous or active/concomitant.

- Prior radiotherapies are defined as those which started prior to the first and single dose of study medication.
- Concomitant radiotherapies are defined as those which:
  - started prior to the first and single dose of study medication and are ongoing or active at the date of the first and single dose of study medication
    OR
  - started on or after the first and single dose of study medication.

13. STUDY MEDICATION EXPOSURE

The following exposure information, as reported in the "68Ga-PSMA-R2 Injection" page of the eCRF, will be

summarized for the FAS and PPS:

- pH
- Radiochemical Purity (%)
- Pre-injection total dose in syringe (MBq)
- Post-injection residual dose in syringe (MBq)
- Total dose injected (MBq)
- Pre-injection volume of solution (mL)
- Post-injection volume of solution (mL)
- Volume of solution administrated (mL)
- Gamma counter calibration factor
- Appearance (Clear and Colourless / Not Clear and Colourless)
- Number of patients with injection interrupted
- Reason for injection interruption

14. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the FAS. Safety will be assessed as the primary objective in this study.

The primary endpoints are defined as:

- Adverse events and serious adverse events (SAEs)
- Absolute changes and changes from baseline in clinical laboratory parameters, vital signs and electrocardiogram (ECG)

14.1. ADVERSE EVENTS

Adverse Events will be coded using the MedDRA central coding dictionary, Version 21.0 or higher.

They will be sorted by decreasing frequency for SOC and for PT within SOC, based on total count.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first and single dose of study medication and until the last actual follow up visit.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-sections below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

14.1.1. All TEAEs

Incidence of TEAEs, and number of events, will be presented by SOC and PT and broken down further by maximum severity and relationship to study medication and study procedure.

14.1.1.1. Severity

Severity is classed as mild, moderate, severe, life threatening/disabling or death. TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

14.1.1.2. Relationship to Study Medication

A related TEAE is defined as a TEAE with a relationship to study medication as "Reasonable possibility" according to the investigator. TEAEs with a missing relationship to study medication will be regarded as related to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

14.1.1.3. Relationship to Study Procedure

A related TEAE is defined as a TEAE with a relationship to study procedure as "Reasonable possibility" according to the investigator. TEAEs with a missing relationship to study procedure will be regarded as related to study procedure. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study procedure will be used in the corresponding relationship summaries.

14.1.2. TEAEs Leading to Discontinuation of Study

TEAEs leading to study discontinuation will be identified by using the "Caused Study Discontinuation" category on the AE page of the eCRF.

For TEAEs leading to study discontinuation, a summary by SOC and PT will be prepared.

AEs leading to study discontinuation will be listed.

14.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF.

A summary of serious TEAEs by SOC and PT will be prepared.

Serious AEs will be listed.

14.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the (e)CRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

AEs leading to Death will be listed.

14.2. Laboratory Evaluations

Results from the local laboratory will be included in the reporting of this study for Hematology, Blood Chemistry and Urinalysis. A list of laboratory assessments to be included in the outputs, and a severity grading system is included in APPENDIX 3.

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Observed values and change from baseline by visit (for quantitative measurements)
- Summary of qualitative clinical laboratory evaluations by visit
- Incidence of abnormal values at any time post-baseline according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements), by visit
- Shift from baseline to worst post-baseline value, according to severity grading system
- Summary of markedly abnormal post-baseline values
- Listing of patients with Grade 3 or above severity grades
- Box plots of absolute values over time and changes from baseline over time

14.2.1. Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the lower and upper limits of the laboratory reference range.
- High: Above the upper limit of the laboratory reference range.

14.2.2. Severity Grading for Laboratory Data

Laboratory results will be classified according to

- *The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Study.*
- *The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03*
- *The University of Delaware Criteria*

The "Grade 0" will be introduced to indicate that a certain laboratory value can be seen as "normal" and does not fulfill the criteria of severity grading either within the reference range or elevated in the other direction than defined in the APPENDIX 3.
Parameters flagged as "Medical Advisor Input Needed" in APPENDIX 3, will be graded as per medical advisor identification based on listings provided [redacted].

14.3. ECG Evaluations

Results from the ECG (Electrocardiogram) will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- RR Interval (msec)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Overall interpretations of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant
    - Abnormal, Clinically Significant

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of markedly abnormal post-baseline values at any time post-baseline.
- Shift from baseline according to worst overall interpretation
- Box plots of absolute values over time and changes from baseline over time
- Listing of patients meeting markedly abnormal criteria

The handling of retests, unscheduled and end of study measurements is described in Section 6.4.

14.3.1. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following

predefined markedly abnormal criteria:

- Absolute values for QT interval, QTcB interval and QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QT interval, QTcB interval and QTcF will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

14.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Weight (kg)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Temperature (^{0}C), considering that °C = (°F - 32) / 1.8
- Heart Rate (bpm)
- Respiratory Rate (resp/min)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of markedly abnormal values at any time post-baseline
- Shift from baseline according to markedly abnormal criteria by visit
- Box plots of absolute values over time and changes from baseline over time
- Listing of patients meeting markedly abnormal criteria

The handling of retests, unscheduled and end of study measurements is described in Section 6.4.

A list of Vital Signs measurements to be included in the outputs, and a severity grading system is included in APPENDIX 4.

14.5. ECOG

ECOG performance status at baseline and post-baseline visits will be listed on the FAS.

15. BIODISTRIBUTION, DOSIMETRY AND IMAGING OF ^{68}GA-PSMA-R2

Biodistribution is defined as the activity in various organs over time quantified by imaging. Dosimetry is the assessment of radiation dose per unit administered activity.

Biodistribution, dosimetry and imaging data are not collected in the CRF. Biodistribution and dosimetry data will be received from the principal scientist of a third-party radiation dosimetry vendor while imaging data will directly be sent from a third-party medical imaging vendor. Results from the radiation dosimetry vendor will be included in the reporting of Phase I of this study. Results from the medical imaging vendor will be included in the reporting of Phase I and II of this study. The analysis of imaging data will also be performed on patients from Phase I.

The terminology, conventional scans and standard imaging, both relate to CT, MRI and/or bone scans.

A list of tests and organs to be included in the outputs is included in APPENDIX 5.

15.1. ANALYSES OF BIODISTRIBUTION AND DOSIMETRY

For phase I, PET and conventional scans will be performed on Day 1 at 20-30 minutes, and 1, 2, and 3 – 4 hours post-injection. For Phase II, all patients will undergo whole body PET and conventional scans optimized for time (up to 2 time points) according to the data analysis from the Phase I component of the study. Further details about imaging assessments can be found in the section 6.5.4 of the protocol.

Data from the radiation dosimetry vendor will be presented using SI Units and the following statistical summaries will be provided:

- Decay corrected tissue activity in normal organs by timepoint
- Non-decay corrected tissue activity in normal organs by timepoint
- Residence times in normal organs
- Absorbed doses, whole body dose and effective dose of 68Ga-PSMA-R2 in normal organs

Time Activity Curve (TAC) will be produced as graphical representation of Decay corrected tissue activity and Non-decay corrected tissue activity.

15.2. ANALYSES OF IMAGING

15.2.1. LABORATORY OPTIMAL THRESHOLD

Standard uptake value (SUV) will only be available in PET scans.

Descriptive analysis will be performed on SUV and the following summaries will be produced:

- SUVmax, SUVmean and TBR with positive lesion status in PET scan
- SUVmax, SUVmean and TBR with positive lesion status in PET scan and correlated with conventional scan
- SUVmax, SUVmean and TBR with positive lesion status in PET scan and not correlated with conventional scan

Lesion Tumor to Background Ratio (TBR) is defined as $SUVmax_{(lesion)}$ / $SUVmean_{(gluteal\ or\ thigh)}$ and will be summarized in the same way as SUV_{max} and SUV_{mean}.

15.2.2. Lesions detected by PET scan and/or conventional scan, by TBR

The number of positive lesions detected by PET scan, correlated or not with conventional scan, will be presented by TBR category.

15.2.3. Burden and location of tumor lesions detected by ^{68}Ga-PSMA-R2 in comparison with conventional imaging modalities such as CT/MRI and/or bone scan.

- The difference of number of lesions detected by ^{68}Ga-PSMA-R2 PET scan and by conventional scan modalities such as CT/MRI and/or bone scan, will be displayed by location. The number of lesions detected on the PET scan, correlated and not correlated with conventional scan lesions, will be presented. The number of lesions detected on the conventional scan, not correlated with lesions detected on the PET scan, will be presented.
- The difference in the number of positive patients detected by ^{68}Ga-PSMA-R2 PET and by conventional scan modalities such as CT/MRI and/or bone scan, will be displayed by location. The number of positive patients detected on the PET scan, with at least 1 lesion correlated, and at least 1 lesion not correlated with a lesion detected on the conventional scan, will be presented. The number of positive patients detected on the conventional scan, with no lesions correlated with any lesion detected on the PET scan, will be presented. Note: A positive patient has at least 1 lesion detected.

15.2.4. Calculation of patient level agreement of ^{68}Ga-PSMA-R2 PET imaging with conventional imaging in prostate cancer patients

The patient level agreement is commonly used to characterize the agreement of a new test with the non-reference standard. Here ^{68}GA-PSMA-R2 PET scan is the new test and conventional scan is the non-reference Standard.

		Conventional Scan	
		+	-
^{68}GA-PSMA-R2 PET Scan	+	a	b
	-	c	d
Total		a+c	b+d

The patient-level positive percent agreement, negative percent agreement and overall percent agreement will be calculated based on the number of patients with at least one positive lesion detected by conventional scan and/or at least one positive lesion detected by PET scan.

These percent agreements will be calculated as follows with their two-sided 95% score confidence intervals:

- Positive percent agreement: a/(a+c) * 100
- Negative percent agreement: d/(b+d) * 100
- Overall percent agreement: (a+d)/(a+b+c+d) * 100

Where

- a is the number of patients with at least one positive lesion detected by conventional scan and at least one positive lesion detected by PET scan
- b is the number of patients with at least one positive lesion detected by PET scan that is not correlated with conventional scan
- c is the number of patients with at least one positive lesion detected by conventional scan that is not correlated with PET scan
- d is the number of patients with no lesions detected by conventional scan or PET scan

These 3 coefficients and their 95% Clopper Pearson Exact confidence intervals will be calculated using SAS PROC FREQ as follow:

```
PROC FREQ data=temp;
  tables resp/binomial (exact level='1');
RUN;
```

The lesion-level positive percent agreement and overall percent agreement will be calculated based on the number of lesions detected as positive by conventional scan and/or by PET scan.

These percent agreements will be calculated as followes with their two-sided 95% score confidence intervals:

- Positive percent agreement: a/(a+c) * 100
- Overall percent agreement: (a)/(a+b+c) * 100

Where

- a is the number of lesions detected as positive in both PET and conventional scan
- b is the number of lesions detected as positive in PET scan but not correlated with conventional scan
- c is the number of lesions detected as positive in conventional scan but not correlated with PET scan

These 2 coefficients and their 95% Clopper Pearson Exact confidence intervals will be calculated using SAS PROC FREQ as above.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

OUTPUT FILE NAMING CONVENTIONS

File names should only consist of lowercase letters, digits (0 to 9) and hyphens. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

The program, program log and output file name should reflect the type of the statistical output. The output files will contain the output number in addition. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. t-14-3-01-1.RTF)

As far as possible, output files should be in RTF and PDF format.

The outputs will be provided in pdf format.

PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter.

The page orientation should preferably be landscape, but portrait is also permitted.

Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.

The number of columns per page (linesize) should be 134 for Letter.

The number of rows per page (pagesize) should be 40 for Letter.

FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining italics or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.

Figures should have a default font of "Times Roman", "Helvetica", or "Courier New".

This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5;
```

HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name and protocol number should appear in row 1, left-aligned
- The output identification number should appear in row 2, left-aligned
- The output title should start in row 2 after output identification number separated by a double dot, left-aligned
- The output population should appear in row 2 after output title separated by a dash, left-aligned. The population should not be spelled out in full, e.g. FAS in preference to Full analysis set.
- Row 3 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)
- Row 4 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g. Vital Signs) followed by metric (e.g. Change from Baseline) e.g. Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form "(N=XXX)"
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left-hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND, if no further specification.
- Numbers in tables should be rounded, not truncated, if no further specification.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization.

- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Patient Number).
- Do not use superscripts and subscripts
- The width of the entire output should match the linesize

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, Std Dev, Median, Q1, Q3, Minimum, Maximum or n, gMean, gCV, Mean, CV, Std Dev, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N
    - Mean, gMean, Q1, Q3, median, gCV% and CV%: N + 1
    - Std Dev: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

  77 (100.0%)
  50 (64.9%)
  0 (0.0%)
- Percentages will be reported to one decimal place, except percentages <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percentages < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
  E.g. (<0.1%)
  (6.8%)
  (>99.9%)
- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data (except for the primary analysis where we compare against a margin with 3 decimal places), and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a semi-colon.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

  (-0.12; -0.10)
  (9.54; 12.91)

P-values:

- P-values should be reported to four decimal places, Rounding will be applied after the <0.0001 and >0.9999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or patient listing.

FIGURE OUTPUT CONVENTIONS

- Figures will be provided in RTF and PDF files using the SAS Output Delivery System (ODS) as generated by SAS.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.
- Boxplots will display whiskers extending from P10 to first quartile and from 3rd quartile to P90.

FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
- The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
- The date/time stamp should appear as footnote 2 at the bottom of the page
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – e.g. "*", "$", "#", "@", "&" and "~".

- The choice of footnote symbols should be consistent. E.g. if you have the footnote "* indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the footer, right aligned.

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes

- Common notes from table to table should appear in the same order.

The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US.

PRESENTATION OF POPULATION GROUPS

For outputs, population groups will be represented as follows and in that order:

Population Group	For Tables, Listings and Graphs
PCa-BR	PCa-BR
mPCa	mPCa
PCa-BR + mPCa	Overall

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Screening
Baseline (Day 1)	D1
Day 7	D7
Day 28	D28

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Population group
- center-patient ID,
- date (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR PROSTATE CANCER HISTORY

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown

ALGORITHM FOR PRIOR / ACTIVE PROCEDURES, RADIOTHERAPIES, CANCER THERAPIES AND MEDICATIONS

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown

General rules:

If start date <= study med start date, assign as prior
If stop date >= study med start date, assign as concomitant

If Missing Stop date: (Rules 2)

If stop date is missing, assign as prior and concomitant

If Missing Start date: (Rules 3)

If stop date < study med start date, assign as prior
If stop date >= study med start date, assign as prior and concomitant

START DATE	STOP DATE	ACTION
Known	Known	General rules
	Partial	General rules
	Missing	General rules
Partial	Known	General rules
	Partial	General rules
	Missing	Rules 2
Missing	Known	Rules 3
	Partial	Rules 3
	Missing	Rules 2

ALGORITHM FOR TREATMENT EMERGENT OF ADVERSE EVENTS

START DATE	STOP DATE	ACTION
Known	Known Partial Missing	If start date < study med start date or start date> actual date of last follow up visit, then not TEAE If start date >= study med start date and start date <= actual date of last follow up visit, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known Partial Missing	Not TEAE
Partial, could be on or after study med start date	Known	Impute start date as earliest possible date, (i.e. first day of month if day unknown or 1st January if day and month are unknown), except if only day is missing and month and year of start date are the same as for study med start date or if day and month are missing and year of start date is the same as for study med start date. In the latter cases, the study med start date will be used for the imputation. If start date <= stop date, then: If stop date < study med start date, then not TEAE If start date > actual date of last follow up visit, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study med start date and start date <= actual date of last follow up visit, then TEAE If start date > stop date, then: Consider the start date as Missing and apply the algorithms for missing start date
	Partial	Impute start date as above. Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of patient's death. In the later case the date of death will be used for imputation. If start date <= stop date, then: If stop date < study med start date, then not TEAE If start date > actual date of last follow up visit, then not TEAE If stop date >= study med start date and start date <= actual date of last follow up visit, then TEAE If start date > stop date, then: Consider the start and stop dates as Missing and apply the algorithms for missing start date
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), if not resulting in a date later than the date of patient's death. In the later case the date of death will be used for imputation: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

Partial date to be imputed as:

Start date	Earliest possible date	first day of month if day unknown or 1st January if day and month are unknown
Stop date	Latest possible date	last day of month if day unknown or 31st December if day and month are unknown

General rules:

If start date <= study med start date, assign as prior
If stop date>= study med start date, assign as concomitant

If Missing Stop date: (Rule 2)

If stop date is missing, assign as prior and concomitant

If Missing Start date: (Rule 3)

If stop date < study med start date, assign as prior
If stop date >= study med start date, assign as prior and concomitant

START DATE	STOP DATE	ACTION
Known	Known	General rules
	Partial	General rules
	Missing	Rule 2
Partial	Known	General rules
	Partial	General rules
	Missing	Rule 2
Missing	Known	Rule 3
	Partial	Rule 3
	Missing	Rule 2

[redacted] Statistical Analysis Plan

APPENDIX 3. LABORATORY ASSESSMENTS

Laboratory parameter		Grading Scale	a) Gradable with Toxicity Grading Scale for Healthy Adult and Adol Volunteers Enrolled in Preventive Vaccine Clinical Study b) Gradable with Common Terminology Criteria for Adverse Events Version 4.03 c) Gradable with University of Delaware Criteria (http://www1.udel.edu/mls/mclane/KMS3RR.html) d) Not Gradable			
						Markedly Abnor
			Grade 1	Grade 2	Grade 3	
Blood chemistry						
ALT / ALAT		a	>=1.1 x ULN – <2.5 x ULN	>=2.5 x ULN – < 5.0 x ULN	>=5.0 x ULN – <10 x ULN	>= 10 x
AST / ASAT		a	>=1.1 x ULN – <2.5 x ULN	>=2.5 x ULN – < 5.0 x ULN	>=5.0 x ULN – <10 x ULN	>= 10 x
Gamma glutamyl transpeptidase (g-GT)		b	>= 1 x ULN – <2.5 x ULN	>=2.5 x ULN – <5.0 x ULN	>=5.0 x ULN – <20.0 x ULN	>=20.0
Total bilirubin	(Liver Function test normal*)	a	>=1.1 x ULN – <1.25 x ULN	>=1.25 x ULN – <1.5 x ULN	>=1.5 x ULN – <1.75 x ULN	>= 1.75
	(Liver Function test increase*)	a	>=1.1 x ULN – <1.5 x ULN	>=1.5 x ULN – <2.0 x ULN	>=2.0 x ULN – <3.0 x ULN	>= 3.0
AP (ALP)		a	>=1.1 x ULN – <2.0 x ULN	>=2.0 x ULN – <3.0 x ULN	>=3.0 x ULN – <10 x ULN	>= 10 x
BUN		a	>=8.211 – <9.75 mmol/L	>=9.75 – <11.625 mmol/L	>= 11.625 mmol/L	Require
Total protein		a	>55 – <=60 g/L	>50 – <=55 g/L	<= 50 g/L	NA
Albumin		a	>27 – <=31 g/L	>25 – <=27 g/L	<= 25 g/L	NA
Glucose	Hyperglycemia	a	>=5.55 – <6.105 mmol/L	>=6.105 – <6.9375 mmol/L	>=6.9375 mmol/L	Insulin hyperos
	Hypoglycemia	a	>=3.6075 – <3.8295 mmol/L	>=3.0525 – <3.6075 mmol/L	>=2.4975 – <3.0525 mmol/L	<2.497
eGFR (Any eGFR value >90 will be classified as Grade 0)		b	<=90 - >60 ml/min/ 1.73 m^2	<=60 - >30 ml/min/ 1.73 m^2	<=30 - >15 ml/min/ 1.73 m^2	<=15 m
LDH		d	NA	NA	NA	NA

[redacted] Statistical Analysis Plan

Laboratory parameter			Grading Scale	a) Gradable with Toxicity Grading Scale for Healthy Adult and Adol Volunteers Enrolled in Preventive Vaccine Clinical Study b) Gradable with Common Terminology Criteria for Adverse Events Version 4.03 c) Gradable with University of Delaware Criteria (http://www1.udel.edu/mls/mclane/KMS3RR.html) d) Not Gradable			
						Markedly Abnor	
				Grade 1	Grade 2	Grade 3	
Corrected Calcium	Hypercalcemia		a	>=2.625 – <2.75 mmol/L	>=2.75 – <2.875 mmol/L	>=2.875 – <3 mmol/L	>= 3 m
	Hypocalcemia		a	>=2 – <2.1 mmol/L	>=1.875 – <2 mmol/L	>=1.75 – <1.875 mmol/L	<1.75 n
Serum creatinine			a	>=132.6 – < 150.28 umol/L	>=150.28 – <176.8 umol/L	>=176.8 – <221 umol/L	>= 221 require
Sodium	Hypernatremia		a	>=144 - <145 mmol/L	>=145 - <147 mmol/L	>=147 - <150 mmol/L	>=150
	Hyponatremia		a	>=132 – <134 mmol/L	>=130 – <132 mmol/L	>=125 – <130 mmol/L	<125 m
Potassium	Hyperkalemia		a	>=5.1 – <5.2 mmol/L	>=5.2 – <5.4 mmol/L	>=5.4 – <5.6 mmol/L	>= 5.6
	Hypokalemia		a	>=3.5 – <3.6 mmol/L	>=3.3 – <3.5 mmol/L	>=3.1 – <3.3 mmol/L	< 3.1 m
Uric acid			b	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	NA	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg mmol/L
Chloride			d	NA	NA	NA	NA
Hematology							
RBC			d	NA	NA	NA	NA
White blood cells with differential	WBC	Increased	a	>=10.8 – <15 10^9/L	>=15 – <20 10^9/L	>=20 – <25 10^9/L	>= 25 1
		Decreased	a	>2.5 – <=3.5 10^9/L	>1.5 – <=2.5 10^9/L	>1 – <=1.5 10^9/L	<= 1 10
	Monocytes		d	NA	NA	NA	NA
	Eosinophils		a	>=0.65 – <1.5 10^9/L	>=1.5 - <5 10^9/L	>=5 10^9/L	Hypere

[redacted] Statistical Analysis Plan

Laboratory parameter		Grading Scale	a) Gradable with Toxicity Grading Scale for Healthy Adult and Adol Volunteers Enrolled in Preventive Vaccine Clinical Study b) Gradable with Common Terminology Criteria for Adverse Events Version 4.03 c) Gradable with University of Delaware Criteria (http://www1.udel.edu/mls/mclane/KMS3RR.html) d) Not Gradable			
					Markedly Abnor	
			Grade 1	Grade 2	Grade 3	
	Basophils	d	NA	NA	NA	NA
	Lymphocytes	a	>0.75 – <=1 10^9/L	>0.5 – <=0.75 10^9/L	>0.25 – <=0.5 10^9/L	<= 0.25
	Neutrophils	a	>1.5 – <=2 10^9/L	>1 – <=1.5 10^9/L	>0.5 –<=1 10^9/L	<= 0.5
Platelets		a	>125 – <=140 10^9/L	>100 – <=125 10^9/L	>25 – <=100 10^9/L	<= 25 1
Hb	(Male) - gm/dL	a	>12.5 – <=13.5	>10.5 – <=12.5	>8.5 – <=10.5	<= 8.5
	(Male) change from baseline value – gm/dL	a	Any decrease – >1.5	>=1.5 – >2.0	>=2.0 – <5.0	>= 5.0
MCV		d	NA	NA	NA	NA
Hematocrit		d	NA	NA	NA	NA
PSA		d	NA	NA	NA	NA
Urinalysis						
Appearance		d	NA	NA	NA	
Color		b	Discoloration	NA	NA	
pH		d	NA	NA	NA	
Specific gravity		d	NA	NA	NA	
Glucose		a	Trace	1+	2+	Hospita hypergl
Occult blood		d	NA	NA	NA	
RBC/hpf		a	>=1 - <10	>=10 – <50	>= 50 and/or gross blood	Hospita packed (PRBC)
WBC/hpf		c	NA	NA	NA	NA
Casts/lpf		c	NA	NA	NA	NA

Document: K:\AAA\Ga-PSMA-R2\VYA27826\Biostatistics\Documentation\SAP\v2.0\Ga-PSMA-R2-SAP_
Author: [redacted]
Template No.: CS_TP_BS016 Revision 5
Effective Date: 01Apr2018

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[redacted] Statistical Analysis Plan

Laboratory parameter	Grading Scale	a) Gradable with Toxicity Grading Scale for Healthy Adult and Adol Volunteers Enrolled in Preventive Vaccine Clinical Study b) Gradable with Common Terminology Criteria for Adverse Events Version 4.03 c) Gradable with University of Delaware Criteria (http://www1.udel.edu/mls/mclane/KMS3RR.html) d) Not Gradable			
				Markedly Abnor	
		Grade 1	Grade 2	Grade 3	
Protein (dipstick test accepted)	a	Trace	1+	2+	Hospita dialysis

* This is not specified in FDA guidance. Therefore, we take as reference to the Hy's Law criteria for potential Function parameters to be taken in to account are Aspartate transaminase (AST) and Alanine transaminase (Al

APPENDIX 4. VITAL SIGNS MEASUREMENTS

Vital Sign parameter		Grading Scale	Gradable with Toxicity Grading Scale for Healthy Adult and Adolescent V Preventive Vaccine Clinical Study Gradable with Common Terminology Criteria for Adverse Events (CTCAE			
					Markedly Abnormal	
			Grade 1	Grade 2	Grade 3	Grade 4
Temperature (°C), considering that °C = (°F - 32) / 1,8		a	>=38.0 – <38.5 °C >=100.4 – <101.1 °F	>=38.5 – <39 °C >=101.1 – <102.0 °F	>=39.0 – <40 °C >=102.0 – <104 °F	>= 40 °C >= 104 °F
Respiratory Rate (resp/min)		a	>=17 – <20	>=20 – <25	>= 25	Intubation
Weight (kg)	Weight gain	b	>=5 - <10% from baseline	>=10 - <20% from baseline	>=20% from baseline	NA
	Weight loss	b	>=5 to <10% from baseline; intervention not indicated	>=10 to <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or total parenteral nutrition (TPN) indicated	NA
Heart Rate (bpm)	Tachycardia	a	>=101 – <115	>=115 – <130	>= 130	Emergency visit or hos for arrhyth
	Bradycardia	a	>50 – <=55	>45 – <=50	<= 45	Emergency visit or hos for arrhyth
Systolic Blood Pressure (mmHg)	Hypertension	a	>=141 – <150	>=150 – <155	>= 155	Emergency visit or hos for maligna hypertensi

[redacted] Statistical Analysis Plan

Vital Sign parameter		Grading Scale	Gradable with Toxicity Grading Scale for Healthy Adult and Adolescent V Preventive Vaccine Clinical Study Gradable with Common Terminology Criteria for Adverse Events (CTCAE			
					Markedly Abnormal	
			Grade 1	Grade 2	Grade 3	Grade 4
	Hypotension	a	>85 – <=89	>80 – <=85	<= 80	Emergency visit or hos for hypote
Diastolic Blood Pressure (mmHg)	Hypertension	a	>=91 – <95	>=95 – <100	>= 100	Emergency visit or hos for malign hypertensi

APPENDIX 5. DOSIMETRY MEASUREMENTS

TEST	Organs / Lesions
Decay corrected tissue activity	Brain
	Heart Wall
	Kidneys
	Lacrimal Glands
	Liver
	Lungs
	Red Marrow
	Salivary Glands
	Spleen
	Thyroid
	Urinary Bladder
	Lesion 1
	...
	Lesion 10
	Percent GI excretion
Non-decay corrected tissue activity	Brain
	Heart Wall
	Kidneys
	Lacrimal Glands
	Liver
	Lungs
	Red Marrow
	Salivary Glands
	Spleen
	Thyroid
	Urinary Bladder
	Lesion 1
	...
	Lesion 10
Absorbed doses	Brain

[redacted] Statistical Analysis Plan

	Heart
	Kidneys
	Lacrimal glands
	Liver
	Lungs
	Red Marrow
	Salivary glands
	Spleen
	Urinary Bladder
Whole body dose	
Effective dose	
Lesion doses	Lesion 1
	...
	Lesion 10
Residence times	Brain
	Heart
	Kidneys
	Lacrimal glands
	Liver
	Lungs
	Red marrow
	Salivary glands
	Spleen
	Thyroid
	Urinary bladder
	Remainder
	Lesion 1
	...
	Lesion 10

Statistical Analysis Plan - V2.0 - 30-Jun-2020

Electronic Signature Manifestation

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Signer Full Name	Meaning of Signature	Date and Time
[redacted]	Document Approval (I certify that I have the education, training and experience to perform this task)	29 Jun 2020 18:41:56 UTC
[redacted]	Document Approval (I certify that I have the education, training and experience to perform this task)	29 Jun 2020 21:10:52 UTC
[redacted]	Document Approval (I certify that I have the education, training and experience to perform this task)	29 Jun 2020 22:07:59 UTC
[redacted]	Document Approval (I certify that I have the education, training and experience to perform this task)	30 Jun 2020 11:14:30 UTC

Official Title:	**A Phase 1/2 open-label, multi-center, safety and tolerability study of a single dose of 68Ga-PSMA-R2 in patients with biochemical relapse (BR) and metastatic prostate cancer (mPCa)**
NCT Number:	NCT03490032
Document Date:	SAP Amendment 1: 03 August 2018

[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT 1
PK ANALYSIS

Advanced Accelerator Applications International SA Study Number: A206D-A01-001
Protocol Version: Version 2.2
Protocol Date: 22 February 2018

[redacted] **Phase Plan Number: ~~00144186~~ 01129004**

A Phase 1/2 open-label, multi-center, safety and tolerability study of a single dose of 68Ga-PSMA-R2 in patients with biochemical relapse (BR) and metastatic prostate cancer (mPCa)

SPONSOR:
Advanced Accelerator Applications International SA
4 rue de la Tour de l'île
1204 Geneva, Switzerland

TESTING FACILITY:
[redacted]
United States

SUMMARY OF CHANGES AND JUSTIFICATIONS

SAP effective date: 03 AUG 2018

Note: When applicable, additions are indicated in bold underlined text and deletions are indicated in bold strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Amendment 1	**Date: 02 OCT 2018**
Throughout Protocol	Updated [redacted] study number; the wrong study number was inadvertently used in the original protocol.
5.2 Corrected terminology regarding Phase I analysis.	Clarified wording.
5.2 Clarified parameter names to match SDTM ver. 3.2 controlled terminology.	Clarified wording.
6 Table added for reporting of compartmental PK parameters	Addition of reporting of compartmental parameters.
9. Amendment Approval	Changed the pharmacokineticist responsible for the phase plan and sample analysis.

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting of pharmacokinetic (PK) data collected under Advanced Accelerator Applications International SA (AAA) protocol Number: A206D-A01-001.

This SAP should be read in conjunction with the study protocol and all applicable Statistical Analysis Plans and/or Workplans for the study. This version of the plan has been developed using the protocol document Version 2.2 dated 22 February 2018. Any further changes to the protocol may require updates to the SAP. Any deviation from this analysis plan will be described in detail in the clinical report. An overall final report of pharmacokinetic data will be prepared and provided by [redacted].

2. OBJECTIVES

The objectives of this study are as follows:

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 Objective:

- 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.

3. EXPERIMENTAL DESIGN

3.1. Overall Study Design and Plan

This study is an open label, multi-center, single dose, safety and tolerability study of a diagnostic radio-pharmaceutical, in subjects with prostate cancer in biochemical relapse and metastatic prostate cancer (mPCa). During Phase 1, approximately 6 subjects will enter the trial unit on the morning of dosing and will remain there for approximately 6 hours post-injection in order to assess the pharmacokinetics (PK), biodistribution vs. time, and dosimetry for critical organs. Serial blood and urine samples will be collected for PK characterization.

Two groups of up to 12 subjects will be enrolled in the second Phase. One group will consist of subjects with prostate cancer in biochemical relapse (PC-BR), while the other will consist of patients with prostate cancer in the metastatic stage (MPs). If preliminary data analysis from the Phase-1 portion of the study returns sufficient data for dosimetry, all Phase-II subjects will have

PET-imaging reduced to 2 whole body scans within the optimal time frame, and blood and urine sampling will be omitted.

Subjects enrolled in the dosimetry set of Phase 1, will enter the trial unit on the morning of the exam. Patients will receive a single dose of 3 MBq/kg, (≥ 150 and ≤ 250 MBq), of ^{68}Ga-PSMA-R2. The product will be prepared prior to administration and injected intravenously and each patient will undergo a dosimetry study based on a series of PET/CT images.

3.2. Planned Pharmacokinetics Sampling Schedule

- Whole blood samples (1 mL in heparinized tubes) will be collected from each of 6 patients during Phase 1 immediately before administration of ^{68}Ga-PSMA-R2 from the opposite arm of drug injection and then at the following approximate time-points following injection: 5 min, 10 min, 20 min, 40 min, 1 h, 2 h, 4 h, and 6 h

- Total urine excreted from each of 6 patients during Phase 1 will be collected pre-injection and as follows post-injection: 0-20 min, 20 min – 1 h, 1 h – 2 h, 2 h -4 h and 4 h – 6 h.

4. GENERAL REPORTING SPECIFICATION:

4.1. Analyses to be Performed

Listings, tables, and graphs that summarize ^{68}Ga-PSMA-R2 whole blood concentrations and pharmacokinetic parameters (as applicable) and ^{68}Ga-PSMA-R2 urine recovery will be created by [redacted]. The data will be compiled into a final pharmacokinetic (PK) report.

4.2. Template and Guidelines to be Followed

Reporting methods generally follow FDA guidelines for clinical data analysis and reporting.

4.3. Statistical Methods Planned

No formal statistical analysis beyond descriptive statistics is planned. Descriptive statistics will include number of observations (N), mean, standard error, geometric mean, %CV geometric mean (coefficient of variation of the geometric mean) calculation, median, min, and max for each parameter, where appropriate.

Blood radioactivity data will be converted into mass concentration data (e.g. ng/mL), considering the specific radioactivity of the product and its radioactive decay. Individual whole blood concentrations will be sorted by dose and subject number and summarized with descriptive statistics using protocol-specified sampling times. Individual pharmacokinetic parameters will be listed by subject number and summarized with descriptive statistics. Both individual and geometric mean profiles of whole blood concentrations of ^{68}Ga-PSMA-R2 will be presented graphically using protocol-specified sampling times. For all analyses, actual blood sampling times will be used in the in the calculation of individual pharmacokinetic parameters.

Missing data will not be imputed except for:

- Tabulation of whole blood concentration data, where concentrations that are below the limit of quantification (BLQ) will be treated as zero.
- Calculation of PK parameters, where BLQ concentrations will be treated as zero.
- Embedded (i.e., BLQ concentrations bracketed by quantifiable data, in a series of concentration measurements constituting a reasonable profile) and/or terminal (after the last measureable concentration) BLQ concentrations will be treated as 'missing'.

Unscheduled measurements will be listed in the individual data listings. Unscheduled measurements will be excluded from the descriptive statistical analysis.

4.4. Software Description

The following software maintained at [redacted] will be used for the analysis:

- Phoenix® WinNonlin® 6.4 for descriptive statistics calculations and non-compartmental analysis and generation of resulting tables. Phoenix WinNonlin 6.4 has been fully validated in the operational environment at [redacted].
- Graphical presentations may be performed using Prism® for Windows, version 5.04.
- Microsoft Excel spreadsheets may be utilized for reporting of interim summary results.
- Final parameter results will be provided in Microsoft Excel spreadsheets and/or SAS transport files. Specification documents will be provided as appropriate.

5. EVALUATIONS:

5.1. General Considerations (Controls, Data Rounding, etc.):

Summary statistics will be presented with the same precision as the original data. Percentages will be presented with one decimal place. Concentrations reported as below the lower limit of quantitation (BLQ) will be set equal to zero for the purpose of analysis. All data will be included in the analysis with the exceptions noted earlier, unless instructions are provided by the Principal Investigator or Bioanalyst to exclude certain data points for cause, e.g. problems during sampling or analysis or some other protocol deviation.

5.2. Non-compartmental Pharmacokinetic Endpoints and Method of Calculation:

Data for individual subjects will be analyzed using non-compartmental methods. The whole blood PK parameters will be estimated from the whole blood concentration-time profiles for all subjects included in the PK analysis set using Phoenix WinNonlin Version 6.4. Actual blood sampling times will be used in the final analyses. Protocol-specified times may be used for ~~interim~~ **PHASE I** analyses **and actual times will be used for Final Analysis**.

In the pharmacokinetic parameter calculations, BLQ concentrations will be treated as zero except for embedded (i.e., BLQ concentrations bracketed by quantifiable data, in a series of concentration measurements constituting a reasonable profile) and/or terminal (after the last measureable concentration) which will be treated as "missing". No attempt will be made to estimate missing PK data.

The percentage of ~~$AUC_{0\text{-}inf}$ extrapolated (%AUCextra)~~ **AUCPEO** will be computed. For values larger than 20%, ~~$AUC_{0\text{-}inf}$~~ **AUCIFO** values will be flagged, but not excluded from the descriptive statistics.

The elimination rate constant (~~kel~~**LAMZ**) will be calculated by least squares linear regression of the terminal portion of the log-transformed whole blood concentration. This terminal range will be determined by visual inspection of the log concentration – time plots. ~~C_{max}~~ **CMAX** will not be used for ~~kel~~ **LAMZ** determination. If adjusted R^2 is lower than 0.80, the elimination rate constant and derived parameters will be flagged but not excluded from the descriptive statistics.

For each PK parameter, summary statistics (including number of subjects, arithmetic mean, geometric mean (for ~~T_{max}~~ **TMAX** no geometric mean will be calculated), SD, CV, median, Min and Max) will be presented.

The following parameters for whole blood will be reported as data permits:

CDISC coded variable names (PPTESTCD)	CDISC variable names (PPTEST)	CDISC definition
AUCLST	**AUC to Last Nonzero Conc**	**The area under the curve (AUC) from the time of dosing to the last measurable concentration.**
AUCLSTD	**AUC to Last Nonzero Conc Norm by Dose**	**The area under the curve (AUC) from the time of dosing to the last measurable concentration divided by the dose.**
AUCIFO	**AUC Infinity Obs**	**The area under the curve (AUC) extrapolated to infinity, calculated using the observed value of the last non-zero concentration.**
AUCPEO	**AUC %Extrapolation Obs**	**The area under the curve (AUC) from the last observed non-zero concentration value to infinity as a percentage of the area under the curve extrapolated to infinity.**
CMAX	**Max Conc**	**The maximum concentration occurring at Tmax.**

TMAX	**Time of CMAX**	**The time of maximum observed concentration sampled during a dosing interval.**
CLO	**Total CL Obs**	**The total body clearance for intravascular administration, calculated using the observed value of the last non-zero concentration.**
RENALCL	**Renal CL**	**The clearance of a substance from the blood by the kidneys.**
VSSO	**Vol Dist Steady State Obs**	**The volume of distribution at steady state based on the observed CLST for a substance administered by intravascular dosing.**
VZO	**Vz Obs**	**The volume of distribution associated with the terminal slope following intravascular administration, calculated using the observed value of the last non-zero concentration.**
LAMZHL	**Half-Life Lambda z**	**Terminal half-life.**
MRTIVIFO	**MRT Intravasc Infinity Obs**	**The mean residence time (MRT) extrapolated to infinity for a substance administered by intravascular dosing, calculated using the observed value of the last non-zero concentration.**
LAMZ	**Lambda z**	**The first order rate constant associated with the terminal (log-linear) portion of the curve.**

- ~~Cmax: maximum whole blood concentration observed~~
- ~~Tmax: Observed time of Cmax~~
- ~~AUC(0-t): area under the concentration-time curve between the time of dose and the last measurable time point.~~
- ~~AUC(0-t)/D: area under the concentration-time curve between the time of dose and the last measurable time point divided by the dose.~~

- ~~λz (Kel): terminal elimination rate constant, determined by linear regression of the terminal points of the log-linear whole blood concentration-time curve~~
- ~~T1/2: elimination half-life, defined as 0.693/λz~~
- ~~AUCinf: total AUC up to the last measurable concentration plus the AUC extrapolated from the last measurable concentration (C_{last} at t_{last}) to infinity: AUC(0-t) +C_{last}/λz~~
- ~~%AUCextrap: the percentage of AUC_{0-inf} that is extrapolated beyond the last measurable concentration: (AUC_{0-inf} – AUC_{0-t})/AUC_{0-inf} *100%~~
- ~~MRT: the mean residence time of ^{68}Ga-PSMA-R2~~
- ~~CL: clearance; calculated as ^{68}Ga-PSMA-R2 Dose/AUC_{0-inf}~~
- ~~Vd: volume of distribution at steady-state; calculated as Mean Residence Time*CL~~
- ~~V_z : volume of distribution during the terminal phase~~

Total recovery of ^{68}Ga-PSMA-R2 in urine will be calculated as well as percent of dose excreted. ~~Renal Cl~~ **RENAL CL** of ^{68}Ga-PSMA-R2 will be estimated as data permit.

Additional parameters will be calculated automatically by Phoenix WinNonlin 6.4 and maintained in the raw data. These additional parameters may be reported at the discretion of the Sponsor and the pharmacokineticist.

5.3. Compartmental Pharmacokinetic Endpoints and Method of Calculation:

For compartmental analysis, an appropriate compartmental model (e.g. a 1 or 2 compartment model) will be fit to the whole blood-concentration time profile using appropriate weighting.

The final compartmental model used to fit the data will be determined as the model that fits the data best. Criteria used to assess the data fit criteria such as visual interrogation of predicted verses observed profiles, correlation coefficient closest to 1.00, and residual Y versus X plots that show residual closest to 0 with no obvious positive or negative bias. Comparisons of different models and weighting schemes may also be evaluated using the Akaike Information criterion (AIC) with the model with the lowest AIC chosen as the best fit. The parameters to be reported based on the compartmental fit will be determined by the actual model used for the fit.

In the event that the data is not sufficient for fitting of a model, only parameters from the non-compartmental analysis will be reported.

6. TABLES AND FIGURES

- Table 1: Summary PK parameters (NCA)
- Table 2: Individual and Mean ^{68}Ga-PSMA-R2 Whole Blood Concentration Versus Time
- Table 3: Individual PK Parameters (NCA)
- **Table 4: Individual and Mean PK Parameters (Compartmental)**
- Table 4**5**: Individual PK Parameters (Compartmental)

- Table ~~5~~**6**: Individual and Mean Concentrations of ^{68}Ga-PSMA-R2 in Urine and Urine Volumes
- Table ~~6~~**7**: Individual and Mean Recovery of ^{68}Ga-PSMA-R2 in Urine and Dose Recovered at Each Interval and Cumulative
- Figure 1: Individual 68Ga-PSMA-R2 Whole Blood Concentration Versus Time Profiles Following IP Injection (linear and semi-logarithmic scale)
- Figure 2: Geometric Mean ^{68}Ga-PSMA-R2 Whole Blood Concentration Versus Time Profiles Following IP Injection (linear and semi-logarithmic scale)
- Figure 3: Individual and Geometric Mean ~~C_{max}~~ **CMAX** Versus ^{68}Ga-PSMA-R2 Dose
- Figure 4: Individual and Geometric Mean ~~AUC(0-t)~~ **AUCLST** Versus ^{68}Ga-PSMA-R2 Dose

Other Tables and Figures may be added at the discretion of the Sponsor and pharmacokineticist

7. QUALITY ASSURANCE

The study will be audited by [redacted] Quality Assurance (QA) in accordance with SOP QA-001 while in progress to assure compliance with applicable Good Laboratory Practice regulations, adherence to the protocol and amendments, if any, and to [redacted] SOPs.

8. REPORTS

There will be a final report generated for this study.

9. AMENDMENT APPROVAL

Sponsor approval received via e-mail on 26 Sep 2018.

[redacted], PhD

02 OCT 2018
Date

[redacted], BS

02 Oct 2018
Date