STATISTICAL ANALYSIS PLAN

Phase II study of preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin Releasing Peptide Receptor

Investigational Product: [^{68}Ga]-NeoBOMB1
Protocol Number: A005D-E01-201 / NCT03724253

Sponsor: Advanced Accelerator Applications

Version Number: 1.0
Date: 11JUN2019

CONFIDENTIAL

SIGNATURE PAGE

Phase II study of preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin Releasing Peptide Receptor

Protocol Number: A005D-E01-201

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

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18/06/19
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Date

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[redacted]
Advanced Accelerator Applications
19/06/2019
Date

[redacted]
[redacted]
20 June 2019.
Date

VERSION HISTORY

Version	Date	Description
1.0	11JUN2019	Initial version

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LIST OF ABBREVIATIONS

[^{68}Ga]	Gallium-68
AE	Adverse Event
$AUC_{(0\text{-}inf)}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
$AUC_{(0\text{-}t)}$	Area under the concentration-time curve from time zero (pre-dose) to some fixed time t
$AUC_{(0\text{-}t)}$/D	AUC(0-t) divided by the dose administered
BC	Breast Cancer
BMI	Body Mass Index
CL	Total systemic clearance for intravenous administration
C_{max}	Maximum concentration observed
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FU	Follow-up
GRPR	Gastrin-Releasing Peptide Receptor
ICF	Informed Consent Form
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	Non-Small Cell Lung Cancer
PC	Prostate Cancer
PD	Progressive Disease
PET	Positron Emission Tomography
p.i.	Post injection

PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QTcB	QT Corrected by Bazett's Formula
QTcF	QT Corrected by Fridericia's Formula
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCLC	Small-Cell Lung Cancer
SI	Standard International unit
SOC	System Organ Class
SUV	Standard Uptake Value
SUVr	Standard Uptake Value ratio
$t_{1/2}$	Half-life
TAC	Time Activity Curve
TEAE	Treatment-emergent Adverse Event
t_{max}	Time of maximum observed drug concentration occurrence
Vd	The apparent volume of distribution of the parent test item in the test system
WHO	World Health Organization

1 INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from Advanced Accelerator Applications Protocol A005D-E01-201. This document is based on protocol Versions 3.1 dated 06 August 2018 (only applicable for France), 3.0 dated 05 July 2018, and 2.0 dated 14 February 2018. If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. However, any revisions to the SAP (both alternative and additional methods) will be made prior to database lock. Reasons for such revisions will be described in the SAP amendment as well as Clinical Study Report (CSR).

2 OVERVIEW

2.1 Objectives

Primary Objective:

- To characterize preliminary targeting properties of [^{68}Ga]-NeoBOMB1 in patients with malignancies known to overexpress Gastrin-Releasing Peptide Receptor (GRPR).

Secondary Objectives:

- To assess safety and tolerability of a single diagnostic dose of [^{68}Ga]-NeoBOMB1 administered as an intravenous bolus injection.
- To assess the bio-distribution, pharmacokinetics, radiation dosimetry, and absorbed dose critical organs for [^{68}Ga]-NeoBOMB1 in a limited number of patients.
- To establish the optimal threshold, expressed as Standardized Uptake Value (SUV), to discriminate Positron Emission Tomography (PET) imaging positive results from negative ones.
- To estimate the [^{68}Ga]-NeoBOMB1 PET lesion-based and patient-based imaging performance relative to a comparable standard imaging.
- To estimate [^{68}Ga]-NeoBOMB1 PET lesion-based and patient-based diagnostic performance relative to cytology and/or histopathology findings (e.g. IHC).

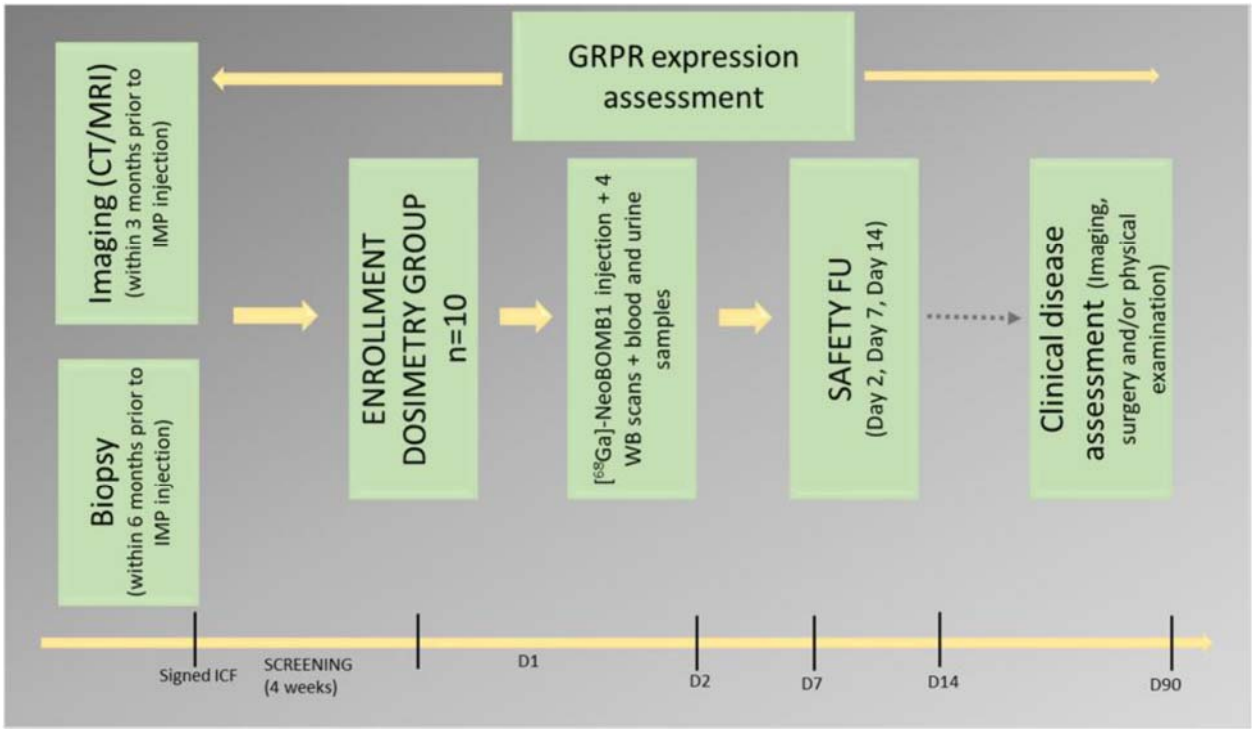
[redacted]

2.2 Trial Design

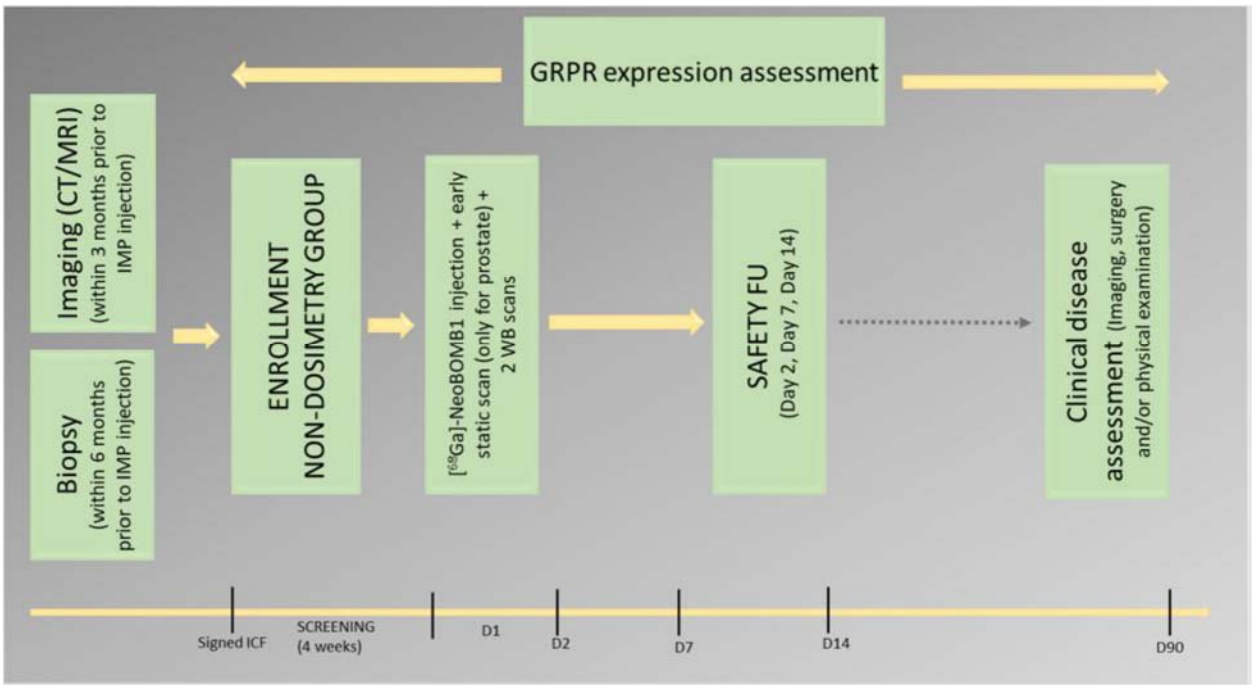
This is a Phase II, multi-center, open label, single dose study in patients with tumor types known to overexpress GRPR, including breast, prostate, colorectal, non-small cell and small-cell lung cancer.

Population will be divided in two groups:

- **Phase-II dosimetry group**: 10 patients bearing breast (n=5 female patients) and prostate cancer (n=5 male patients) will undergo additional assessments to confirm previous data on tracer bio-distribution, radiation dosimetry, residence time for critical organs, and absorbed dose critical organs for [^{68}Ga]-NeoBOMB1. Patients enrolled in the dosimetry group in France will be relapsed or refractory breast and prostate cancer. Serial venous whole blood and urine samples will be collected for activity-based pharmacokinetic characterization. Patients will undergo 4 15-min-static whole-body PET scans at 15 min, 1h±15 min, 2h±15 min and 4h±30 min post injection (p.i.) to determine absorbed doses to normal organs and to target tumor lesions. Venous whole blood samples will be collected at pre-dose (0), 5, 10, 20, 30±5, 60±5 min, and at 2h±10 min and 3-4 h±10 min p.i. Urine samples at pre-dose, from 0-2 h and from 2-4 h p.i. will also be collected.



- **Phase-II non-dosimetry group:** 40 patients bearing breast cancer (n=5), prostate cancer (n=5), colorectal cancer (n=10), NSCLC (n=10), SCLC (n=10). PET-imaging will be reduced to 2 whole body scans at 1h30±30min and at 2h30±30min likely to be a 15-min static late PET for all tumor-types. Only prostate tumor patients will undergo an additional early 5-min static PET scan to better assess lymph node metastases (if applicable). Blood and urine sampling will be omitted.



GRPR expression must be assessed while the study is ongoing within 4 weeks after IMP injection by Immunohistochemistry staining from archival or recent biopsy specimens (not older than 6 months prior to IMP injection).

All study objectives, with the exception of the secondary one relative to bio-distribution and dosimetry that will be assessed only within the dosimetry group, will be assessed in the overall population (n=50). Analyses of the dosimetry group data will lead to the optimal time window for PET/CT imaging for future clinical trials. However, in the case that the Sponsor obtains the results of the dosimetry and bio-distribution assessments from at least 3 patients of the dosimetry group before the full completion of the study recruitment and the results show that the optimal time window is different from 1h30±30min or 2h30±30min as initially predicted by the Sponsor, the time points of the whole-body PET/CT scans for the remaining patients included in the non-dosimetry group will be adjusted.

2.3 Study Assessments

For the detailed schedule of expected events and study procedures to be conducted at each visit and time point, please refer to Section 4.5 in the protocol. The schedule of assessments for dosimetry group is different from that of non-dosimetry group due to one additional study objective pertaining to the bio-distribution and dosimetry.

3 STUDY ENDPOINTS

3.1 Primary Study Endpoints

- Number and location of tumor lesions detected by [^{68}Ga]-NeoBOMB1 overall and for each tumor type
- Calculation of the ratio tumor/background SUV and %ID/g and calculation of absorbed dose (uGy/MBq) in tumor overall and for each tumor type

3.2 Secondary Study Endpoints

- Standard safety parameters (clinical monitoring, laboratory, and ECG)
- Tolerability and safety of the administration of a diagnostic dose of [^{68}Ga]-NeoBOMB1 in patients with malignancies known to overexpress GRPR as determined by absence of:
  - increased number of SAEs compared to other peptide-based radiotracers;
  - clinically relevant changes of physiological parameters (blood pressure, heart rate, and ECG findings)
- Generation of decay corrected tissue time-activity curves (TACs) from [^{68}Ga]-NeoBOMB1 PET/CT images in normal organs and tumor lesions.
- Quantification of urinary excretion of [^{68}Ga]-NeoBOMB1
- Calculation of half-life of [^{68}Ga]-NeoBOMB1 in blood
- Generation of non-decay-corrected TACs from [^{68}Ga]-NeoBOMB1 PET/CT images in normal organs and tumor lesions
- Calculation of residence times in critical organs and tumor lesions of [^{68}Ga]-NeoBOMB1
- Calculation of absorbed doses in critical organs and effective whole body dose of [^{68}Ga]-NeoBOMB1
- Calculation of pharmacokinetic (PK) parameters, such as maximum concentration observed (C_{max}), time of maximum observed drug concentration occurrence (t_{max}), area under the concentration-time curve from time zero (pre-dose) to some fixed time t [$AUC_{(0-t)}$], AUC(0-t) divided by the dose administered [$AUC_{(0-t)}$/D], half-life ($t_{1/2}$), area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [$AUC_{(0-inf)}$], total systemic clearance for intravenous administration (CL), the apparent volume of distribution of the parent test item in the test system (Vd)
- Number and location of tumor lesion detected by [^{68}Ga]-NeoBOMB1 in comparison with comparable standard imaging modalities such as FDG-PET
- Calculation of the [^{68}Ga]-NeoBOMB1 PET overall, positive and negative agreement on a lesion-by-lesion basis as well as on a patient basis relative to the standard imaging overall and for each tumor type
- Comparison of number of patients with tumor lesions detected by [^{68}Ga]-NeoBOMB1 with cytology and/or histopathology from archival and/or recent biopsy specimens

- Calculation of the [^{68}Ga]-NeoBOMB1 PET sensitivity and specificity on a lesion-by-lesion basis for all lesions with associated biopsy data, and on a patient basis relative to histopathology / cytology data

[redacted]

4 ANALYSIS POPULATIONS

4.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all patients who enter the study and receive the [^{68}Ga]-NeoBOMB1 dose. The safety set in this case is identical to the FAS and so will not be defined as a separate set.

4.2 Per Protocol Set

The Per Protocol (PP) Set consists of all patients of the FAS who complete the study according to the protocol with no major protocol violations (i.e. CSR reportable violations as specified in the Protocol Deviation Plan).

The list of subjects to be excluded from the PP Set will be finalized prior to database lock.

All analyses will primarily be performed on the FAS, and selected analyses may be repeated on the PP Set if there are sufficient number of violations to warrant it. Deviation of results by using the PP Set will be discussed.

5 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

The primary focus of the statistical analysis will be on descriptive statistics and graphical presentations of data. Continuous variables will be presented as numbers 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. Continuous variables will be compared where relevant (by point estimates and confidence intervals) using the most appropriate approach such as paired analysis Mann-Whitney-Wilcoxon U statistic or paired analysis Student's *t* statistic. Proportions will be compared using the appropriate test statistic among Chi-squared test statistic, Fisher exact test statistic or McNemar test statistic. Point estimates and confidence intervals will also be computed when feasible. 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.

All analyses will be performed using SAS® Version 9.3 or later (SAS Institute Inc., Cary NC).

All data presentations will be presented primarily by the overall population but may also be repeated split by tumor type where relevant. Some presentations will also be repeated split by whether or not the patient was found to have tumors bearing GRPR expression according to cytology and/or histopathology findings.

5.1 Definition of Study Day

Study day will be calculated relative to the date of [^{68}Ga]-NeoBOMB1 administration as follows:

- Assessment/event date – date of [^{68}Ga]-NeoBOMB1 administration + 1, if assessment/event date is on or after the date of [^{68}Ga]-NeoBOMB1 administration;
- Assessment date/event date – date of [^{68}Ga]-NeoBOMB1 administration, if assessment/event date is before the date of [^{68}Ga]-NeoBOMB1 administration.

Note that under the convention specified above, there will be no Study Day 0.

5.2 Baseline Definition

Baseline value for any given variable is defined as the last assessment obtained prior to the initiation of the [^{68}Ga]-NeoBOMB1 administration.

5.3 Unscheduled Visits

In general, by-visit summaries will be presented by the scheduled visits (visit number and corresponding visit name of planned clinical encounter). Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of "Unscheduled". Such visits will be included in data listings and will contribute to the derivations of the best, worst, minimum, or maximum values where required.

5.4 Handling of Missing Data

Missing/Partial Dates:

- In cases of incomplete dates (e.g. AEs and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. No imputation of start/end dates or times will be performed.
    - If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered both a prior and a concomitant medication.
    - If the partial AE onset date/time information does not indicate that the event started prior to or after the treatment, the event will be classified as treatment-emergent.

- Time from first diagnosis of primary cancer (months) is calculated as (date of administration of the study drug - date of first diagnosis + 1)/30.4375. If the month and year of the first diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation.
- Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

Other Missing Values: Missing values for other individual data points will remain as missing unless otherwise specified. Missing values will not be imputed and only observed values will be used in data analyses and presentations unless otherwise stated.

5.5 Multicenter Studies

The center effect will not be considered for this study.

5.6 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be conducted.

5.7 Other Data Handling Approaches

For continuous variables, the estimated mean, median, and quartiles for a set of values will be displayed to one more decimal place than that of the majority of the individual measurements, and the standard deviation will be printed out to 1 additional place. P-values will be given with 4 decimals (i.e., 0.xxxx). When a p-value is less than 0.0001, '<0.0001' will be displayed.

All fractional numeric values will be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3 etc.). Percentage values will be printed with 1 digit to the right of the decimal point (e.g., 52.3%, 8.9% etc.).

6 ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

6.1 Subject Disposition and Analysis Populations

Subject disposition and analysis populations will be tabulated for each tumor type and in total when feasible. Otherwise, summary will be tabulated in total.

The number of screened subjects (the ones who sign the ICF) and the number of screen failures along with the primary reason of screen failure will be tabulated. Similarly, the number of subjects in the Full Analysis Set and the Per Protocol Set will be summarized.

The following subject disposition categories will be summarized for all enrolled subjects:

- Number of subjects who received the treatment and completed the study,

- Number of subjects who received the treatment but discontinued from the study.

For subjects who discontinued from the study, the primary reason for discontinuation will be summarized.

All deaths that occur during the study will be reported in a subject-level data listing, which will include subject demographics, dates of the IMP administration, cause of death, and the number of days between IMP administration and death.

All subject disposition data will be presented in data listings.

6.2 Protocol Deviations

Protocol deviations will be captured in the study. The protocol deviation plan provides the definition of the protocol deviation in this study, for CSR reportable and CSR non-reportable.

Protocol deviations and violations will be reviewed and any subject data that will be excluded from the PP analyses due to major protocol violations will be determined prior to database lock.

6.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively based on the Full Analysis Set for each tumor type and in total, and may be repeated on the PP Set if deemed appropriate.

Sex and race will be summarized by the number and percentage of subjects in each category. Age at informed consent (years), weight, height and body mass index (BMI) at baseline will be presented with summary statistics (n, mean, standard deviation, minimum, median, quartiles, and maximum).

Baseline disease characteristics will be summarized descriptively. Time from initial (first) diagnosis of primary disease (months) and time from initial (first) diagnosis of metastasis (months) will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, quartiles, and maximum). Diagnostic stage, diagnostic tumor stage, diagnostic node stage, and diagnostic metastasis stage will be summarized to show the number and percentage of subjects in each category.

Time from initial diagnosis of primary disease or metastasis will be calculated as follows:

(Date of IMP administration – Date of initial diagnosis + 1)/30.4375

Data listings of subject demographic and baseline disease characteristics will be provided.

6.4 Prior and Concomitant Therapies/Medications

Prior and concomitant medications and cancer therapies/medications will be coded using WHO Drug. Prior and concomitant cancer surgeries, concomitant medical procedures/non-drug therapies will be coded using MedDRA. Dictionary versions will be updated biannually.

Prior medications, therapies, surgeries, or procedures are defined as those which started prior to the start of the IMP administration.

Concomitant medications, therapies, surgeries, or procedures are defined as those received by the subject on or after the start of IMP administration.

The following variables will be tabulated on FAS (for each tumor type and in total) to characterize the extent of prior cancer treatments:

- Prior cancer therapies/medications (yes, no);
- Number of prior cancer therapy/medication lines (0, 1–2, ≥ 3);
- Number of prior cancer therapy/medication lines (as a continuous variable);
- Number of treatment cycles to the most recent prior therapy/medication line (as a continuous variable);
- Best response to the most recent prior cancer therapy/medication line (CR, PR, SD, PD, or Not Evaluable);
- Prior radiotherapy (yes, no); and
- Prior cancer-related surgery (yes, no).

The number and percentage of subjects treated with concomitant cancer therapy/medications, cancer surgery, medications, or medical procedures/non-drug therapies will be summarized based on FAS. Medications and cancer therapies/medications will be summarized by anatomic therapeutic class (ATC) and preferred term (PT) for each tumor type and in total. Cancer surgery and medical procedures/non-drug therapies will be similarly summarized by system organ class (SOC) and PT.

The subject data on all (prior and concomitant) cancer therapy/medications, radiotherapy, cancer surgery, medications, and medical procedures/non-drug therapies will be provided as data listings.

6.5 Medical History

Medical history will be coded using MedDRA version available at the time (updated biannually). The number and percentage of subjects will be summarized by SOC and PT based on Full Analysis Set for each tumor type and in total.

All subject-level medical history data will be provided as data listings.

6.6 Dosing

All study drug administration data will be listed by subject.

7 ANALYSIS OF EFFICACY

Efficacy analyses will be performed primarily on the Full Analysis Set, but may be repeated on the PP Set if deemed appropriate. In general, the efficacy results will be presented overall, as well as split by tumor type and by GRPR positive and negative (if at least one GRPR-negative patient is enrolled).

7.1 Number and Location of Lesions Identified by [^{68}Ga]-NeoBOMB1 by PET Imaging

The preliminary targeting properties of [^{68}Ga]-NeoBOMB1 will be assessed by summarizing the number and location of lesions identified by PET overall and split by GRPR positive and negative patients, as well as by tumor type.

The number and location of lesions identified by aforementioned PET imaging will be compared with the number and location of lesions identified by the comparable conventional imaging.

7.2 Evaluation of Targeting Properties by Standard Uptake Value (SUV)

Targeting properties of [^{68}Ga]-NeoBOMB1 will also be evaluated by PET imaging using tumor uptake. Tumor uptake will be evaluated by the Standard Uptake Value (SUV) at each lesion by PET Imaging. The maximum SUV_{mean} and SUV_{max} (g/mL) of each lesion will be presented by the lesion location with summary statistics (n, mean $\pm$ standard deviation, minimum, median, quartiles, and maximum) at scheduled time points overall and split by GRPR positive and negative patients, as well as by tumor type. Dosimetry and non-dosimetry group will be summarized separately due to different scheduled time points.

The 80% and 95% confidence intervals for difference in SUV (SUV_{mean} and SUV_{max}) between GRPR positive and negative patients will be derived by Student's *t* distribution if normality assumption is adequate, or Wilcoxon Rank Sum method otherwise.

The Standard Uptake Value ratio (SUVr) at each time point will be calculated as the SUV_{mean} of each lesion / the SUV_{mean} of different regions as a reference and presented in a data listing.

7.3 Dosimetry and PK Analyses

Dosimetry calculations will be issued from the analyses of organs receiving the highest dose of [^{68}Ga]-NeoBOMB1, identified visually. Regions of Interest (ROIs) or Volumes of Interest (VOIs) will be placed over these organs to determine relative radiotracer uptake, calculated as a percentage of the injected dose per gram of tissue (%ID/g). Tissue time-activity curves with quantitative fractions of administered activity will be generated from the amount of radioactivity in one given tissue at a given moment over the amount of radioactivity present in the blood at that given moment and integrals will be calculated accordingly through dynamic acquisitions. Time activity curves ([TAC] - (u(t) in % injected dose per gram of tissue), describing %ID/ROI of the activity amount injected vs. time will be derived, considering renal excretion activity. Tissue activity curves will be fitted to mono- and bi-exponential curves to yield cumulative activities. Urine samples from 0-2h and from 2-4h post-injection will be collected to complete

dosimetry and biodistribution assessments. The absorbed dose (µGy/MBq) will be transformed into formal biological equivalent dose for radiation exposure (µSv/MBq) to finally yield an effective radiation dose, a factor between others that could help providing an estimation of total danger to the whole organism.

The absorbed dose in tumor and the effective radiation dose will be summarized with descriptive statistics (n, mean, standard deviation, minimum, median, quartiles, and maximum).

In addition, PK parameters such as C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-t)}$/D, $t_{1/2}$, $AUC_{(0-inf)}$, CL, Vd) will be listed and summarized using descriptive statistics.

Further details regarding Dosimetry calculations and analyses will be provided in a separate report by Rapid Dosimetry.

7.4 Diagnostics by [^{68}Ga]-NeoBOMB1 Compared with Conventional Imaging

The diagnostic performance of [^{68}Ga]-NeoBOMB1 to malignancies (lesions) known to overexpress GRPR will be paralleled with comparable standard imaging modalities such as, but not limited to, FDG-PET. Positive and negative lesions by the two imaging techniques will be cross-tabulated overall and also by localization area on a lesion level and a patient level, where positivity will be assessed visually. Cross-tabulations will also be repeated splitting by GRPR positive and negative patients and also by primary tumor type of patients.

7.4.1 Lesion-Level Analyses of Diagnostics by [^{68}Ga]-NeoBOMB1 Compared with Conventional Imaging

At lesion level, overall, positive, and negative agreement of [^{68}Ga]-NeoBOMB1 will be calculated based on the aforementioned tabulations as follows:

- Overall agreement = 100% x (Double positive + Double negative) / total number of patients who underwent both imaging procedures
- Positive agreement = 100% x Double positive / (Double positive + Comparator single positive)
- Negative agreement = 100% x Double negative / (Double negative + Comparator single negative)

The McNemars test may also be performed to assess the level of discordance between the two imaging techniques where appropriate, acknowledging issues with lack of independence of observations on a lesion level. The odds ratio and its confidence intervals (80% and 95%) will be computed for overall result and for each tumor type. The same calculation will be computed for GRPR positive and negative, if feasible.

7.4.2 Patient-Level Analyses of Diagnostics by [^{68}Ga]-NeoBOMB1 Compared with Conventional Imaging

At patient level, positive agreement of [^{68}Ga]-NeoBOMB1 will be defined as the proportion of patients with at least one positive lesion detected by conventional imaging (i.e. all patients included in the trial) who also have at least one positive lesion detected by [^{68}Ga]-NeoBOMB1 PET imaging

7.5 Diagnostics by [^{68}Ga]-NeoBOMB1 Compared to Histological Evidence

The diagnostic performance of [^{68}Ga]-NeoBOMB1 to malignancies (lesions) known to overexpress GRPR will be compared with cytology and/or histopathology findings from archival and/or recent biopsy specimens.

Since the biopsy is only performed on one lesion, a direct link may not be possible if there are multiple lesions per organ identified on [^{68}Ga]-NeoBOMB1-PET. In this event, the determination of positive versus negative lesions on [^{68}Ga]-NeoBOMB1-PET will be done at organ level, i.e., if any lesion is positive in that organ, then the organ will be considered positive.

7.5.1 Lesion-Level Analyses of Diagnostics by [^{68}Ga]-NeoBOMB1 *in vivo* Imaging versus Histology

At lesion level, positive and negative lesions on [^{68}Ga]-NeoBOMB1-PET will be cross-tabulated with histological assessment of GRPR expression according to biopsy data. The cross-tabulations will be done for overall results and for each tumor type. Sensitivity and specificity values will be calculated for each two-way contingency table displayed. Furthermore, the odds ratio and its confidence intervals (80% and 95%) by McNemars test will be computed at each two-way contingency table. The sensitivity and specificity will be calculated as follows:

- Sensitivity = 100% x True positive / (True positive + False negative)
- Specificity = 100% x True negative / (True negative + False positive)

7.5.2 Patient-Level Analyses of Diagnostics by [^{68}Ga]-NeoBOMB1 *in vivo* Imaging versus Histology

At patient level, patients with at least one positive lesion on [^{68}Ga]-NeoBOMB1-PET versus those without positive lesions on [^{68}Ga]-NeoBOMB1-PET will be cross-tabulated with positive or negative results of GRPR expression by histological analyses. The cross-tabulations will be done for overall results and for each tumor type. Sensitivity and specificity values will be calculated for each two-way contingency table displayed. The sensitivity and specificity will be calculated as follows:

- Sensitivity = 100% x True positive / (True positive + False negative)
- Specificity = 100% x True negative / (True negative + False positive)

7.5.3 Relationship between [^{68}Ga]-NeoBOMB1 Diagnostics and GRPR Expression Level

Histological assessment of GRPR expression and the diagnostic performance of [^{68}Ga]-NeoBOMB1 may be compared. The scatter plot of GRPR expression versus *in vivo* imaging

sensitivity (proportion of conventional imaging lesions also detected by [^{68}Ga]-NeoBOMB1 PET imaging) on patient level will be generated, and the strength of association will be properly assessed. If the assumption of linear relationship seems adequate, the Pearson's correlation coefficient will be computed. Otherwise, Spearman's rank-order correlation coefficient will be derived.

The correlative analyses between [^{68}Ga]-NeoBOMB1 diagnostic performance and GRPR expression level will be conducted for each tumor type and for all available data.

8 ANALYSIS OF SAFETY

Safety analyses will be summarized based on FAS and split by tumor type and in total unless otherwise specified.

8.1 Adverse Events

AEs will be coded using MedDRA version available at the time (updated biannually).

Treatment-emergent adverse events (TEAEs) are defined as AEs that start on or after the initiation of IMP administration.

Intensity of all adverse events will be graded according to the Toxicity Grading Scale in vaccine clinical trials. Adverse events not listed in the Toxicity Grading Scale in vaccine clinical trials should be graded as guided in study protocol.

An overview of AEs will be provided which summarizes subject incidence of the following information:

- Any TEAEs,
- Drug-related TEAEs,
- Grade 3/4/5 TEAEs,
- Drug-related grade 3/4/5 TEAEs,
- Deaths due to AEs,
- Treatment-emergent SAEs,
- Drug-related treatment-emergent SAEs,
- Dose interruption due to TEAEs, and
- Dose interruption due to drug-related TEAEs.

The number and percentage of subjects with TEAEs will be summarized by SOC and PT. Drug-related TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, TEAEs leading to dose interruption of study drug, and drug-related TEAEs leading to dose interruption of study drug will be summarized in the same manner. For these summaries, subjects with multiple adverse

events will be counted only once per SOC and PT. Note that drug-related AEs include the AEs which either definitely, probably, or possibly related to study drug.

Summaries will be provided by the worst toxicity grade, SOC, and PT for the number and percentage of subjects with TEAEs and drug-related TEAEs. For these summaries, subjects with multiple adverse events will be counted only once by the worst toxicity grade within each SOC and PT.

Data listings will be provided for SAEs, grade 3/4/5 AEs, AEs leading to dose interruption, Hypersensitivity (SMQ) AEs, and AEs leading to death. A by-subject AE data listing including, but not limited to, verbatim, PT, SOC, toxicity grade, action taken, outcome, and relationship to study drug will be provided.

8.2 Safety Laboratory Parameters

Descriptive statistics will be provided at baseline and each scheduled visit for selected clinical laboratory test results (chemistry, hematology, and coagulation) and changes from baseline to each scheduled visit will be derived. The minimum post-baseline value, maximum post-baseline value, and last post-baseline value will be summarized in the same manner, where both scheduled and unscheduled post-baseline values will be considered for the derivations.

Laboratory values will be assigned toxicity grades when available using the Toxicity Grading Scale in vaccine clinical trials. Directional shifts in laboratory toxicity grades (comparing baseline grade with the worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of subjects and their maximum grade shift. For parameters without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation. Both scheduled and unscheduled post-baseline values will be considered when deriving the minimum/maximum/worst post-baseline assessment.

Clinical laboratory tests will also be tabulated by the number and percentage of subjects in each abnormal category (abnormal but not clinical significant, abnormal and clinical significant) for each parameter at each scheduled visit and for the worst post-baseline assessment.

Laboratory test results will also be presented graphically in terms of box plots of absolute values over time and changes from baseline over time.

All clinical laboratory data will be listed by subject using the International System of units (SI units). Values outside the normal ranges will be flagged.

8.3 Vital Signs

Descriptive statistics will be provided for the vital signs measurements (systolic blood pressure, diastolic blood pressure and heart rate) and changes from baseline, if available, at each scheduled visit. The minimum post-baseline value, maximum post-baseline value, and last post-baseline value will be summarized in the same manner, where both scheduled and unscheduled post-baseline values will be included for deriving the minimum/maximum/last post-baseline value.

Vital signs results will also be presented graphically in terms of box plots of absolute values over time and changes from baseline over time.

All vital sign measurements will be listed by subject at each scheduled visit.

8.4 ECG Parameters

Electrocardiogram parameters (PR, RR, QRS, QT, QTcF, and QTcB) will be summarized using descriptive statistics for actual values and for change from baseline at each scheduled visit. The minimum post-baseline, maximum post-baseline, and last post-baseline value will be summarized in the same manner, where both scheduled and unscheduled post-baseline measurements will be considered for deriving the minimum/maximum/last post-baseline value.

Note that Frederica's and Bazett's correction to the reported QT interval, QTcF and QTcB, respectively, will be derived (in milliseconds) for all subjects and time points as follows:

$$\text{QTcF (msec)} = \frac{\text{QT(msec)}}{\sqrt[3]{\text{RR(msec)}/1000}};\ \text{QTcB (msec)} = \frac{\text{QT(msec)}}{\sqrt{\text{RR(msec)}/1000}}$$

The number and percentage of subjects with elevated QTcF and QTcB during the post-baseline period will be presented for the following categories: QTcF or QTcB worsening to >450 msec, >480 msec, and >500 msec from baseline, and increase in QTcF or QTcB from baseline >30 msec and >60 msec.

Overall interpretations of ECG assessment will be tabulated by the number and percentage of subjects in each category (normal, abnormal but not clinically significant, abnormal and clinically significant, not evaluable, or unknown) at each visit and at worst post-baseline assessment.

Electrocardiogram parameters results will also be presented graphically in terms of box plots of absolute values over time and changes from baseline over time.

All ECG measurements and overall interpretation will be listed by subject.

8.5 Physical Examinations

Physical examination results will be listed by subject.

8.6 Other Safety Parameters

All other variables will be presented in by-subject data listings when data is available.

9 INTERIM ANALYSIS

No formal interim analysis is planned for this study.

10 SAMPLE SIZE AND POWER CONSIDERATIONS

The primary objective of the trial is to assess preliminary targeting properties of [^{68}Ga]-NeoBOMB1. Data for this objective will be reported descriptively therefore no formal statistical sample size calculation is feasible. It is anticipated that 50 patients with malignancies known or suspected to overexpress GRPR will be recruited in the trial and will be administered [^{68}Ga]-NeoBOMB1 prior to PET-CT imaging. According to histopathology data, a great percentage of these patients is expected to be GRPR positive. However, some patients will also be recruited whose tumors do not show GRPR positive expression by histopathology/cytology data. This will allow calculation of preliminary diagnostic characteristics and the sample size should allow reasonable precision around estimations of targeting properties. For instance, if a patient level sensitivity of 83.3% is observed (for e.g. if 25 patients had lesions detected by [^{68}Ga]-NeoBOMB1 imaging out of 30 patients in the trial with GRPR positive histopathology/cytology) the 95% CI around this would be 66.4% to 92.7%.

The overall sample size of 50 patients will be fixed to ensure 10 patients are recruited within each of the tumor types included in the trial. Although it won't be possible to make strong conclusions within the tumor types, this should ensure that a reasonable number of GRPR positive patients are available within each tumor type and this will allow initial estimates of diagnostic properties to be made and will ensure each tumor type is fairly represented.

Ten patients will be recruited to the dosimetry sub-population of the trial. This is considered sufficient to obtain data on dosimetry, bio-distribution and dose-limiting critical organs. Data from all 50 patients in the trial will be used to assess all other study objectives.

11 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The protocol did not specifically mention that SUVr would be calculated. SUVr will be derived by the statistics group and presented in a data listing.

Since the biopsy data only contains biopsies of one lesion per subject, comparison of the number of tumor lesions detected by [68Ga]-NeoBOMB1 with cytology and/or histopathology from archival and/or recent biopsy specimens will not be performed.