Study Protocol	
Protocol Number	A005D-E01-201 / NCT03724253
EudraCT Number	2017-003432-37
Investigational Product	[^{68}Ga]-NeoBOMB1 50 µg, kit for radiopharmaceutical preparation
Active substance	NeoBOMB1
Radiolabelled Imaging Product	[^{68}Ga]-NeoBOMB1
Trial Phase	Phase II
Trial Title	Phase II study of preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin Releasing Peptide Receptor
Short Trial Title	NeoFIND - [^{68}Ga]-NeoBOMB1 imaging in patients with malignancies known to overexpress GRPR
Version and Date	v.3.0. dated 05 July 2018
Trial Sponsor	Advanced Accelerator Applications
The concepts and information contained herein or generated during the study are considered proprietary and shall not be disclosed in whole or in part without the expressed written consent of Advanced Accelerator Applications.	
This study is to be completed according to the guidelines of Good Clinical Practice (GCP) and conducted in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.	

SPONSOR SIGNATORY APPROVAL PAGE

PROTOCOL TITLE: 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

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

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INVESTIGATOR ENDORSEMENT PAGE

I agree to conduct the study as outlined in the protocol entitled *"Phase II study of preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin-Releasing Peptide Receptor."* in accordance with the guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

1. Permission to allow the Sponsor and the regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures participant confidentiality. If this study is to be inspected by a regulatory agency, the Sponsor should be notified as soon as possible;

2. Submission of the proposed clinical investigation, including the protocol and the consent form to a duly constituted Ethic Committee (EC) as well as competent authorities for approval and acquisition of written approval prior to study conduct;

3. Use of written informed consent that is obtained prior to study conduct and that contains all the elements of consent as specified in the federal regulations and has been previously approved by the Sponsor, the EC and the Competent Authority (CA);

4. Submission of any proposed change in or deviation from the protocol to the EC to be approved by the Sponsor. Any proposed changes or deviations from the protocol may require that the informed consent also reflect such changes or deviations and that the revised informed consent be approved by the EC and competent authority;

5. Documentation and explanation of individual protocol deviations on the appropriate case report form page or in letters to the Sponsor;

6. Reports of serious adverse events to the Sponsor/CRO (Contract Research Organisation) within 24 hours by telephone and a written report of the serious adverse event within 72 hours after the Investigator's initial receipt of the information;

7. Reporting of Serious Adverse Events (SAE) according to ICH/GCP (International Conference Harmonization/ Good Clinical Practices) and regulator standards. SAE will be reported from the signing of the informed consent and followed until resolution or determined to be not clinically significant;

8. Submission of timely progress reports to the EC and Sponsor at appropriate intervals on a schedule determined by the EC.

Regulations require an Investigator to prepare and maintain adequate and accurate case histories designed to record all observations and other data (such as investigational product accountability) pertinent to the investigation on everyone enrolled in the study. These records

must be maintained by the Investigator for a minimum period of 15 years or a period of time determined by the Sponsor following the date a marketing application is approved for the indication for which it is being investigated, or, if no application is to be filed or if the application is not approved for such indication, a minimum of 15 years or a period of time determined by the Sponsor after the investigation is discontinued and the appropriate regulatory authorities are notified.

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

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

Principal Investigator Signature	Date of Signature

Content

List of abbreviations

AE	Adverse Event
AC	Activity Curves
ADR	Adverse Drug Reaction
BC	Breast Cancer
CA	Competent Authority
CNS	Central Nervous System
e-CRF	Electronic Case Report Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CT	Computed Tomography
DSUR	Drug Safety Update Report
EC	Ethic Commitee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
eGFR	estimated Glomerular Filtration Rate
ER	Estrogen receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
[^{18}F]-FDG	18-fluorodeoxyglucose
GCP	Good Clinical Practice
GIST	Gastro Intestinal Stromal Tumour
GMP	Good Manufacturing Practice
GRP	Gastrin-Releasing Peptide
GRPR	Gastrin-Releasing Peptide Receptor
Hb	Hemoglobin
HCl	Hydrogen Chloride

HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITLC	Instant Thin Layer Chromatography
ITT	Intention To Treat
LN	Lymph Node
LPLV	Last Patient Last Visit
MBq	Mega Becquerel
MIRD	Medical Internal Radiation Dose
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NMB	Neuromedin B
NOAEL	No Observed Adverse Effect Level
NSCLC	Non–Small Cell Lung Cancer
PC	Prostate Cancer
PET	Positron Emission Tomography
p.i.	Post injection
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PT	Prothrombin Time
PTT	Partial Thromboplastin Time

PV	Pharmacovigilance
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
QTc	frequency-corrected QT-time
RBC	Red Blood Cell
RCP	Radiochemical Purity
ROI	Region of Interest
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
mSv	milliSievert
SUSAR	Suspected Unexpected Adverse Reaction
SUV	Standardized Uptake Value
TAC	Time Activity Curve
TBR	Target to background ratio
TKI	Tyrosine-Kinase Inhibitor
TMF	Trial Master File
WBC	White Blood Cell
WHO	World Health Organization
VOI	Volume Of Interest

Definitions

- Pre-screening:

The pre-screening is the period before the signature of the Informed Consent Form (ICF).

- Screening:

The screening period starts at the time of signature of ICF and ends on the day of IMP injection.

- Enrollment:

A subject is enrolled when he/she is administered with the Investigational Medicinal Product (IMP).

- IMP phase:

The IMP phase starts when IMP is administered to a subject, i.e. if a subject has entered the IMP phase, it means this subject has been injected with [^{68}Ga]-NeoBOMB1.

- Screening failure:

A screening failure occurs when a subject who has signed the ICF (i.e. screened/enrolled subject) does not enter the IMP phase (i.e. injected subject).

1 Study Synopsis

Clinical Study [^{68}Ga]-NeoBOMB1 – EudraCT Number: 2017-003432-37		
Version date	July, 05th , 2018	**Version 3.0**
Study number	A005D-E01-201	**Clinical phase: II**
Investigational Medicinal Product	[^{68}Ga]-NeoBOMB1 50 µg, kit for radiopharmaceutical preparation	
Title of the study	Phase II study of preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in adult patients with malignancies known to overexpress Gastrin Releasing Peptide Receptor.	
Study centres	Multi-center study	
Sponsor	Advanced Accelerator Applications	
Potential Indication	Diagnosis and or monitoring of tumours known to overexpress GRPR.	
Rationale	GRP is a bombesin-like peptide growth factor implicated in the regulation of numerous central and peripheral functions. By binding to a GRP extracellular receptor (GRPR), it activates an intracellular G-protein that triggers further chain reactions. Beside its physiological widespread role, GRP has been demonstrated to be a potent mitogen for normal and neoplastic tissues and may be involved in growth dysregulation and carcinogenesis. In fact, upregulation of GRP/GRPR has been reported in several cancers, including breast, prostate, colon, lung (small cell and non-small cell), stomach, pancreas, uterus, ovaries, head and neck squamous cell cancer and in various central nervous system malignancies. For instance, GRPR expression has been investigated in primary and metastatic breast cancer among different molecular subtypes. GRPR overexpression was most strongly associated with estrogen receptor (ER) positivity and found in over 75% of the primary tumour samples and in over 90% of their metastatic lymph nodes. In parallel, a massive GRP receptor overexpression has been demonstrated in prostate tissues that are already neoplastic or in the process of malignant transformation (i.e. prostatic intraepithelial neoplasias). In this specific case, GRP receptors have been thought of as markers for early molecular events in prostate carcinogenesis and useful in differentiating prostate hyperplasia from prostate neoplasia. In the lung, GRP has been found in the pulmonary neuroendocrine cells and is responsible for lung development and maturation. Nevertheless, GRP has also been reported in relation to growth dysregulation and carcinogenesis on non–small cell lung cancer (NSCLC) proliferation. In fact, increased levels of	

	GRP have led to increased release of pro-ligands for epidermal growth factor receptor (EGFR) with subsequent activation of EGF and mitogen-activated protein kinase downstream pathways. Presence of GRP and/or expression GRPR have also been investigated in colorectal cancer samples (primary tumour, lymph nodes and metastatic lesions) where over 80% samples expressed GRP/GRPR as opposed to adjacent normal healthy epithelium. Overall, the literature accounts with a growing body of evidence suggesting that GRPR might be a valuable target. Peptide receptor agonists have long been the ligands of choice for tracer development and utilization in nuclear medicine thanks to their high radioactive accumulation inside the target cells after receptor-radioligand complex internalization. However, GRPR antagonists have been compared to GRPR agonists and showed greater tumour uptake and better image contrast. Furthermore, GRPR antagonists allow for a safer clinical use, since no acute biological adverse effects are expected. The Sponsor has therefore designed the current protocol to establish whether the ligand NeoBOMB1, a high affinity antagonist for GRPR, radiolabelled with a well-established PET isotope, Gallium-68 (^{68}Ga) is a suitable radiotracer for *in vivo* detection of GRPR-expressing malignancies, currently focusing on breast, prostate, lung (small cell and non-small cell) and colon-rectum.
Objectives	**Primary Objective** • To characterize preliminary targeting properties of [^{68}Ga]-NeoBOMB1 in patients with malignancies known to overexpress 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 doses in critical organs for [^{68}Ga]-NeoBOMB1 in a limited set 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 imaging performance lesion-based and patient-based relative to a comparable standard imaging practice (eg PET, CT) according to the tumour type. • To estimate the [^{68}Ga]-NeoBOMB1 PET diagnostic performance lesion-based and patient-based relative to the GRPR histopathology

	findings (e.g. IHC) [redacted]
Study design	This is a Phase II, multi-center, open label, single dose study in patients with tumour types known to overexpress GRPR, including breast, prostate, colorectal, non-small cell lung (NSCL) and small-cell lung (SCL) cancer. Population will be divided into two groups: • a **Phase-II dosimetry group**, accounting with 10 patients (splitted into breast cancer: n=5 female patients and prostate cancer: n=5 male patients) who will undergo several 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. Venous whole blood and urine samples will be collected for activity-based pharmacokinetics characterization; • a **Phase-II non-dosimetry group,** accounting with 40 patients splitted into : ✓ Breast cancer: n=5 ✓ Prostate cancer: n=5 ✓ Colorectal cancer: n=10. ✓ NSCLC: n=10 ✓ SCLC: n=10 Patients included in the non-dosimetry group will undergo one early and one late whole-body PET-imaging acquisition, with no blood and urine sampling. Only prostate tumour patients will undergo an additional early 5-min static PET scan to better assess lymph node metastases (if applicable). 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). The objectives of the study will be applicable for the whole study population with the exception of the secondary objective relative to the biodistribution and dosimetry that will be applicable only for the dosimetry group.
PET Imaging Data acquisition	The subjects enrolled in the **dosimetry group** will undergo 4 15-min static whole-body PET scans at 15 min, 1h±15 min, 2h±15 min and at 4h±30 min post injection (p.i.) to determine absorbed doses to normal organs and to target tumour lesions. Regions of Interest (ROIs) or Volumes of Interest (VOIs) will be drawn on the late whole-body PET images over the critical organs and tumour lesions to generate tissue time-activity curves (TACs), calculate the tumour-background ratio and assess the radioactivity residence times. To determine blood activity curves, venous whole blood samples will be withdrawn (around 0, 5, 10, 20, 30, 60 min, 2 h and 3-4 h p.i.) and assessed

	via γ-counter for radioactivity measurements. Urine samples from 0-2 h and from 2-4 h p.i. will be collected and assessed *via* γ-counter for radioactivity measurements to complete dosimetry and biodistribution assessments. Urine samples will be saved, frozen for further metabolite assessments, at the Sponsor's decision. The subjects enrolled in the **Phase II non-dosimetry group** will undergo whole-body PET acquisitions at 1h30±30min and at 2h30±30min, likely to be a 15-min static PET for all tumour-types combined with a 5-min-static early-PET for prostate cancer.
CT Imaging Data Acquisition	For all patients a low-dose CT will be combined to PET imaging.
Data analysis, biodistribution and dosimetry	**<u>Dosimetry group:</u>** ROIs/VOIs for critical organs and tumour lesions will be drawn using the acquired static PET images resulting in tissue TACs with quantitative fractions of administered activity. ROIs/VOIs will be drawn over these organs to determine relative radiotracer uptake calculated as a percentage of the injected dose per gram of tissue (%ID/g). Tissue TACs will be generated from the amount of radioactivity in one given tissue considering renal excretion activity. Tissue TACs will be fitted to mono- and bi-exponential curves to yield cumulative activities and residence times will be calculated. Dosimetry calculations will be issued from the analyses of organs receiving the highest dose, identified visually. 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. **<u>All patients:</u>** Maximum standardized uptake values (SUV_{max}) will be used to determine the tumour lesions, defined as focal areas of abnormal uptake featuring greater SUV_{max} than that of surrounding tissue. The imaging time points characterized by the greatest number of lesions will be identified *via* qualitative visual analysis. Similarly, the greatest SUV values will be determined for each lesion on all scans *via* semi-quantitative analysis. Malignant-like lesions compatible per tumour type and localisation will be semi-quantified and expressed as SUV_{mean} and SUV_{max}. All lesions will be counted and analyzed by measuring SUV_{mean} and SUV_{max} and relative background. Clinical assessment (surgery, imaging or physical examination) during 3 months after IMP injection will be collected if available for patients to

	correlate the focal uptake of [^{68}Ga]-NeoBOMB1 PET which was not possible be matched to morphological lesions on CT/MRI.
Safety	Safety assessments including physical examination, vital signs, Electrocardiogram (ECG) with frequency-corrected QT-time (QTc) assessment, routine blood analysis and urinalysis will be performed prior to [^{68}Ga]-NeoBOMB1 administration on all subjects. **Dosimetry group:** twelve-lead ECG readings and vital signs will be checked pre-dose, immediately after the radiotracer administration, at 30 min, after the last whole-body scan (around 4h) and during the FU visits scheduled at Day 2 (24h p.i.), Day 7±1, and Day 14±2 for physical examination, routine blood analysis, urinalysis, vital signs and ECG. **Non-dosimetry group**: twelve-lead ECG readings and vital signs will be checked at pre-dose and at 30 min after the administration. At Day 2, the FU visit will be a phone call to assess potential adverse events, allergic reactions and concomitant treatments. The FU visits of Day 7±1 and Day 14±2 account for physical examination, routine blood analysis, urinalysis, vital signs and ECG. Visit at Day 7±1 is optional and can be replaced by a phone call to only assess potential adverse events, allergic reactions and concomitant treatments. The emergence of any Adverse Event (AE) and Serious Adverse Event (SAE) will be monitored and recorded during trial conduct. Adverse events will be graded per the Toxicity Grading Scale in vaccine clinical trials.
Tracer	NeoBOMB1 will be radiolabelled locally following a predefined procedure using a solution of ^{68}Ga in hydrochloric acid (HCl) provided by a ^{68}Ge/^{68}Ga generator to obtain [^{68}Ga]-NeoBOMB1 as radiolabelling imaging product for intravenous injection. The dose of [^{68}Ga]-NeoBOMB1 to be injected is 3MBq/kg ±10%, no less than 150 MBq and no more than 250 MBq. This amount of radioactivity is sufficient for Quality Control (QC) testing and quality imaging with [^{68}Ga]-NeoBOMB1. [^{68}Ga]-NeoBOMB1 will be administered according to applicable regulation (including local regulations, International Commission on Radiological Protection (ICRP) Publication 62 and Radiation protection 99).
Planned number of subjects	Fifty patients bearing malignancies known to overexpress GRPR originating from either breast, prostate, lung (small-cell and non-small cell) or colon-rectum will be enrolled. Population will be divided into 2 groups: the dosimetry group will include 5 patients with breast cancer and 5 patients with prostate cancer, who will undergo further assessments for dosimetry calculations. The non-dosimetry group will include 40 patients. Patients will be splitted into : ✓ Breast cancer: n=5

	✓ Prostate cancer: n=5 ✓ Colorectal cancer: n=10. ✓ NSCLC: n=10 ✓ SCLC: n=10
Inclusion and exclusion criteria	**Main Inclusion Criteria** 1. Subjects must be at least 18 years of age 2. Subjects must have signed and dated an informed consent prior to any study-specific procedures. 3. Subjects with histologically-confirmed tumour, for whom a less than 6-month-old biopsy has been performed. 4. Dosimetry group: • Luminal breast cancer • Adenocarcinoma of the prostate 5. Non-dosimetry group: • Luminal breast cancer • Adenocarcinoma of the prostate • Small-cell lung cancer • Non-small cell lung cancer • Colorectal carcinoma 6. At least one malignant lesion detected *via* functional or morphological imaging (PET combined to appropriate tracer according to tumour type, CT, MRI) within 3 months prior to the administration of [^{68}Ga]-NeoBOMB1. 7. The Eastern Cooperative Oncology (ECOG) performance status 0-2. 8. Subjects must agree to use highly effective methods of contraception (female partners of male participants should use highly effective methods of contraception) during the trial. **Main Exclusion Criteria** 1. Renal insufficiency or an estimated Glomerular Filtration Rate (eGFR) <50 ml/min/1.73m^2. 2. Haematological toxicity grade > 2 (Toxicity Grading Scale in vaccine clinical trials) 3. Participation in any other investigational trial within 30 days of study entry. 4. Subjects with positive pregnancy test (Urine dipstick), and/or currently breast-feeding 5. Concurrent severe illness or clinically relevant trauma within 2 weeks before the administration of the investigational product that might preclude study completion or interfere with study results. 6. Concurrent bladder outflow obstruction or unmanageable urinary incontinence.

	7. Known or expected hypersensitivity to ^{68}Gallium, NeoBOMB1, or any excipient present in [^{68}Ga]-NeoBOMB1. 8. Any condition that precludes raised arms position 9. Prior administration of a radiopharmaceutical within a period corresponding to 8 half-lives of the radionuclide. 10. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.
Study duration and Assessments	The study will have a duration of approximately 6 weeks, with a pre-injection phase of 4 weeks, including the screening/baseline assessment period, the injection and PET visit on Day 1, 3 safety follow-up visits post-administration of investigational drug on Day 2, Day 7±1 and Day 14±2. If available, data generated from routine clinical disease follow-up assessments within 3 months from IMP injection will be collected. The study assessments are described in the Visits Schedules and assessment, section 4.5.
Study periods	A) The **Screening period** will last 28 days (Day -28 to -1) or less per subject and includes the **Screening Visit** to obtain informed consent and establish protocol eligibility. B) The **injection and PET day** is [^{68}Ga]-NeoBOMB1 administration day (Day 1) and differs according to groups. For the **dosimetry group,** it includes 7 time-points: **pre-dose, 0-5 min, 5-15 min, 30 min, 1h, 2h, 3-4h** p.i.**.** For the **non-dosimetry group**, it includes 4 time-points: **pre-dose**, **injection** (0-5 min), **1h30±30min p.i**. and **2h30±30 min** p.i. C) The **safety follow-up period** lasts for 14 days from PET day. It includes FU visits on **Day 2, Day 7±1, and Day 14±2** for all subjects**.** D) The **optional routine clinical follow-up** will start on D14±2 follow-up visit and will last up to 3 months from IMP injection according to clinical disease assessment.
Statistical methods	All statistical analyses will be primarily descriptive in nature and will include summaries and graphical presentations of data. All data presentations will be presented by the overall population but may also be repeated split by tumour type where relevant. Some presentations will also be repeated split by whether or not the patient was found to have tumours bearing GRPR expression according to cytology and/or histopathology findings. The preliminary targeting properties of [^{68}Ga]-NeoBOMB1 will be assessed by summaries of number and location of lesions identified by PET, SUV values per lesion, tumour background ratio of [^{68}Ga]-NeoBOMB1 and the percentage of injected dose reaching the target presented split by GRPR positive and negative patients. Tumour uptake will be evaluated by Standard Uptake Value. SUV_{mean} and SUV_{max} will be determined and summarized descriptively. Adverse events will be listed on an individual basis and summarized by System Organ Class and Preferred term including relationship and severity.

	Clinical laboratory parameters, vital signs, and ECG parameters will be summarized and presented graphically as observed values and changes form baseline at each measuring time. Clinical laboratory parameters will also be analysed in terms of tabulations of values to within, below or above normal ranges provided by the laboratory of each site. Descriptive statistics and graphical presentations will be produced for bio-distribution, radiation dosimetry data as appropriate. Number of observed tumour lesions and localization in PET/CT will be compared to number of observed lesions and localization in a comparable conventional imaging by GRPR positive and negative patients. Positive and negative lesions by the two imaging techniques will be cross tabulated overall and by localization area on a lesion level and a patient level and overall, positive and negative sensitivity agreement calculations and tests of association will be performed where appropriate overall and split by GRPR positive and negative patients. This will also be repeated splitting by primary tumour type of patients in the trial. The preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 relative to cytology and/or histopathology findings from archival and/or recent biopsy specimens will be assessed primarily on a patient level, but also on a lesion level for lesions with associated biopsy data available. Sensitivity and specificity calculations will be performed by cross tabulating GRPR positive or negative patients according to cytology data with whether those patients had lesions detected by PET imaging. Appropriate tests of association may also be performed if relevant.

2 Introduction

2.1 Background

Gastrin-releasing peptide (GRP), a bombesin-like peptide growth factor, regulates numerous functions of the gastrointestinal and central nervous systems, including release of gastrointestinal hormones, smooth muscle cell contraction, and epithelial cell proliferation. It is a potent mitogen for physiologic and neoplastic tissues, and it may be involved in growth dysregulation and carcinogenesis.
The effects of GRP are primarily mediated through binding to its receptor, the GRP receptor (GRPR), a G protein–coupled receptor originally isolated from a small cell lung cancer cell line. Upregulation of the pathway of GRP/GRPR has been reported in several cancers, including breast, prostate, uterus, ovaries, colon, pancreas, stomach, lung (small and non-small cell), head and neck squamous cell cancer and in various cerebral and neural tumours.
In breast cancer, GRPR overexpression can reach very high density according to tumour type (e.g. 70-90 % expression in ductal breast cancer specimens) [1]. GRPR are highly overexpressed in prostate cancer where studies in human prostate cancer cell-lines and xenograft models showed both high affinity (nM level) and high tumour uptake (%ID/g) but the relative expression of GRPR across evolving disease setting from early to late stage has not been fully elucidated yet [2]. In colorectal patients, presence of GRP and expression of GRPR have been determined by immunohistochemistry in randomly selected colon cancers samples, including LN and metastatic lesions. Over 80% of samples aberrantly expressed either GRP or GRPR, and over 60% expressing both GRP and GRPR, whereas expression was not observed in adjacent normal healthy epithelium [3].
GRP is physiologically present in pulmonary neuroendocrine cells and plays a role in stimulating lung development and maturation. However, it seems to also be involved in growth dysregulation and carcinogenesis. Stimulation of GRP leads to increasing the release of epidermal growth factor receptor (EGFR) ligands with subsequent activation of EGFR and mitogen-activated protein kinase downstream pathways. Using non–small cell lung cancer (NSCLC) cell lines it has been confirmed that EGF and GRP both stimulate NSCLC proliferation, and inhibition of either EGFR or GRPR resulted in cell death [4].

In nuclear medicine, peptide receptor agonists have long been the ligands of choice for tracer development and utilization. The rationale behind the use of agonist-based constructs laid on to receptor-radioligand complex internalization enabling the high accumulation of radioactivity inside the target cells. In case of radiometal-labelled peptides, the efficient receptor-mediated endocytosis in response to agonist stimulation provides high *in vivo* radioactivity uptake in targeted tissues, a crucial prerequisite for optimal imaging of malignancies. However, a paradigm shift occurred when receptor-selective peptide antagonists showed preferable biodistribution, including considerably greater *in vivo* tumour uptake, compared with highly potent agonists. A further advantage displayed by GRPR antagonists is a safer clinical use, not so much at tracer doses for the current diagnostic point of view, but in view of greater doses for potential therapeutic purposes, as the use of antagonists does not foresee acute biological adverse effects [5].

The Sponsor has therefore designed the current protocol to establish whether the ligand NeoBOMB1, a high affinity antagonist for GRPR, radiolabelled with a well-established PET isotope, Gallium-68 (^{68}Ga) is a suitable radiotracer for *in vivo* detection of GRPR-expressing malignancies, currently focusing on breast, prostate, lung (small cell and non-small cell) and colon-rectum.

2.2 Preclinical data

Bombesin was first isolated from the European frog Bombina bombina and was demonstrated to mimic the mammalian gastrin-releasing peptide (GRP) and neuromedin B (NMB)[6].
In non-clinical models, [^{68}Ga]-NeoBOMB1 have shown high affinity to the GRPR expressed in breast, prostate, and Gastro Intestinal Stromal Tumour (GIST), as well as a low degree of internalization upon binding to the specific receptor. The ability of the radiolabelled peptide to target the GRPR expressing tumour has been confirmed in *in vivo* imaging studies in both prostate cancer and GIST models.

2.3 Clinical data

2.3.1 Clinical studies performed with Bombesin analogues

Various bombesin-analogs have been studied in several entities, including both agonists and antagonists. The following summary tables (Table 1, 2, 3) provide the reference to each study.

Table 1: Studies with in-human application of bombesin and its analogs in prostate cancer.

Bombesin analogue	**Indication**	**Dose**	**Summary of Results**
[^{68}Ga]-NeoBOMB1 (antagonist)	Prostate adenocarcinoma	60-339 MBq	First in man study – compassionate use program. Good tolerability, good sensitivity: visualization of liver micrometastatis and lymph-node metastases down to 5 mm in size (n=4). [7] See protocol section 2.3.2
[^{68}Ga]-SB3* (antagonist)	Advanced prostate cancer (breast cancer also included) with progressing disease and history of previous therapy, including hormonal.	283.91±91 MBq 23±0.7 nmol (~35 µg)	17 pts (9 PC + 8 BC): 5 out of 9 (~55%) prostate cancer patients showed specific uptake. [8]

^{18}F-BAY-86-4367 (antagonist)	Primary and recurrent prostate cancer	302±11 MBq	First in man study. PK/dosimetry in patients was good. Positive PET images in 3/5 with primary disease and 2/5 with biochemical relapse (n=10). [9]
^{64}Cu-CB-TE2A-AR06 (antagonist)	newly diagnosed prostate cancer (T1c-T2b, GS 6-7) without prior therapy	184±51 MBq 14±4 µg	Phase I study. PK/dosimetry was ok. Three out of 4 tumours were visualized with high contrast. [10]
[^{68}Ga]-BAY-86-7548 (also called RM2) (antagonist)	histologically confirmed prostate adenocarcinoma or recurrent prostate cancer	147 MBq (median dose) ~20 µg	First in man study (n=14): sensitivity, specificity, and accuracy of 88%, 81% and 83%, respectively, for detection of primary PCa and sensitivity of 70% for metastatic LNs (histology as gold standard). [11]
	biochemically recurrent prostate cancer	na	Pilot comparison of ^{68}Ga-RM2 and ^{68}Ga-PSMA-11 PET (n=7). ^{68}Ga-PSMA-11 had the highest physiologic uptake in the salivary glands and small bowel, with hepatobiliary and renal clearance, whereas ^{68}Ga-RM2 had the highest physiologic uptake in the pancreas, with renal clearance. ^{68}Ga-PSMA-11 localized in a lymph node and seminal vesicle in a patient with no abnormal ^{68}Ga-RM2 uptake. Abdominal periaortic lymph nodes were more easily visualized by ^{68}Ga-RM2 in two patients because of lack of interference by radioactivity in the small intestine. [12]
^{99m}Tc-HABBN (agonist)	biopsy-proven prostate cancer	549–688 MBq	SPECT/CT results were negative (most likely due to metabolic instability of the compound). GRPR expression confirmed by IHC. (n=8) [13]
^{99m}Tc-[Leu13] BN (agonist)	Suspected or proven prostate cancer	185 MBq	Positive SPECT scans obtained in all 8 patients with cancer (total of 10 examined, 2 with benign adenoma). Invasion of pelvic LNs shown in 3 cases (confirmed at surgery). [14]
^{99m}Tc-RP527 (agonist)	Metastasized prostate cancer	555 MBq	First in man study with bombesin analogue including 4 patients with metastasized PC. Specific uptake observed in 1 out of 4. [15]

[^{68}Ga]-RM1	biopsy-proven prostate cancer	111-142 MBq	Pre-surgical newly diagnosed prostate cancer patients (n=7). High physiologic uptake in the pancreas and quick renal clearance. High and specific uptake in primary cancer lesions was found. The SUVmean and SUVmax of tumour region is 4.22±1.33 and 4.64±2.53. Median tumour to background ratios was 15.29 (9.27-26.42). [16]

Table 2: Studies with in-human application of bombesin and its analogs in breast cancer.

Bombesin analogue	**Indication**	**Dose**	**Summary of Results**
[^{68}Ga]-BAY-86-7548 (also called RM2) (antagonist)	biopsy-proven primary breast carcinoma	118 – 213 MBq (26 – 56 µg of peptide)	High contrast in 73% examined breast cancer patients (n=15). Sensitivity of 93% for ER-positive tumours, upstaging in 47% of patients. [17]
[^{68}Ga]-SB3 (antagonist)	Advanced breast cancer (prostate cancer also included) with progressing disease and history of previous therapy	283.91±91 MBq 23±0.7 nmol (~35 µg)	Mixed patients with prostate (n=9) and breast (n=8) cancer: 4 out of 8 breast cancer patients showed specific uptake. [8]
^{99m}Tc-Bombesin analogue (not specified)	Suspicious palpable breast lesions (with no definitive diagnosis in other imaging procedures)	370–444 MBq	SPECT/CT scan findings were positive in 19/33 patients. Pathologic examination confirmed breast carcinoma in 12 patients with positive scan. Sensitivity (100%); specificity (66.1%); negative (100%) and positive (63%) predictive values; accuracy (76%). [18]
^{99m}Tc-EDDA/HYNIC-[Lys3]-BBN (agonist)	Early stage breast cancer and healthy volunteers.	na	Rapid blood clearance with mainly renal excretion. Good dosimetry. Well-differentiated concentration of tracer in cancer mammary tissue. [19]
^{99m}Tc-RP527 (agonist)	Clinical diagnosis suggestive of breast carcinoma (n=9) and tamoxifen-resistant bone-metastasized	~555 MBq (max 3ng/kg)	Tracer uptake evident in the primary tumour in 8 out of 9 pts (88%) and in involved lymph nodes (confirmed by IHC). In the 5 patients with tamoxifen-resistant osseous disease, none (0/5) of the known

	breast carcinoma (n=5)		sites of osseous involvement were positive. [20]
^{99m}Tc-[Leu13] BN (agonist)	breast cancers (T1b and T1c)	185-296 MBq (~0.7 mg)	The tracer detected all 5 breast cancers, with visualization of axillary nodes where present. When comparison with Sestamibi, BN analogue showed higher T/B. [21]

Table 3: Studies with in-human application of bombesin and its analogs in GIST and other types of cancer.

Bombesin analogue	**Indication**	**Dose**	**Summary of Results**
[^{68}Ga]-NeoBOMB1 (antagonist) – AAA kit	GIST	150-250 MBq	See protocol section 2.3.2
[^{68}Ga]-BZH3 (agonist)	Low Grade Gliomas	na	[^{68}Ga]-bombesin and [^{18}F]FDG-PET predicted correctly malignant transformation or recurrence of the initial tumour (n=9). [22]
[^{68}Ga]-BZH3 (agonist)	GIST	150-210 MBq (~ 3 nmol)	Patients with GIST (n=17 scheduled for therapy with imatinib because of unresectable primary or recurrent GIST or because of metastatic disease). Dynamic PET scans comparison with [^{18}F]FDG. FDG discovered 25/30 lesions, BZH3 8/30. Once, the lesion was seen with BZH3 and not with FDG. [23]
^{99m}Tc-[Leu13] BN (agonist)	Colorectal cancer	na	13 (6 suspected colon cancer +7 known to have rectal cancer). Cancer detected in 11/13 and 2 false positives. 5/5 positive lymph nodes detected. Results confirmed by pathologic evaluation. [24]
[^{68}Ga]-NOTA-Aca-BBN	Healthy volunteers Glioma diagnosed by MRI	111 ± 148 MBq	Healthy volunteers (n=4): no adverse symptoms being noticed or reported. Patients with glioma (n=12): all MRI-identified lesions showed high signal intensity on ^{68}Ga-

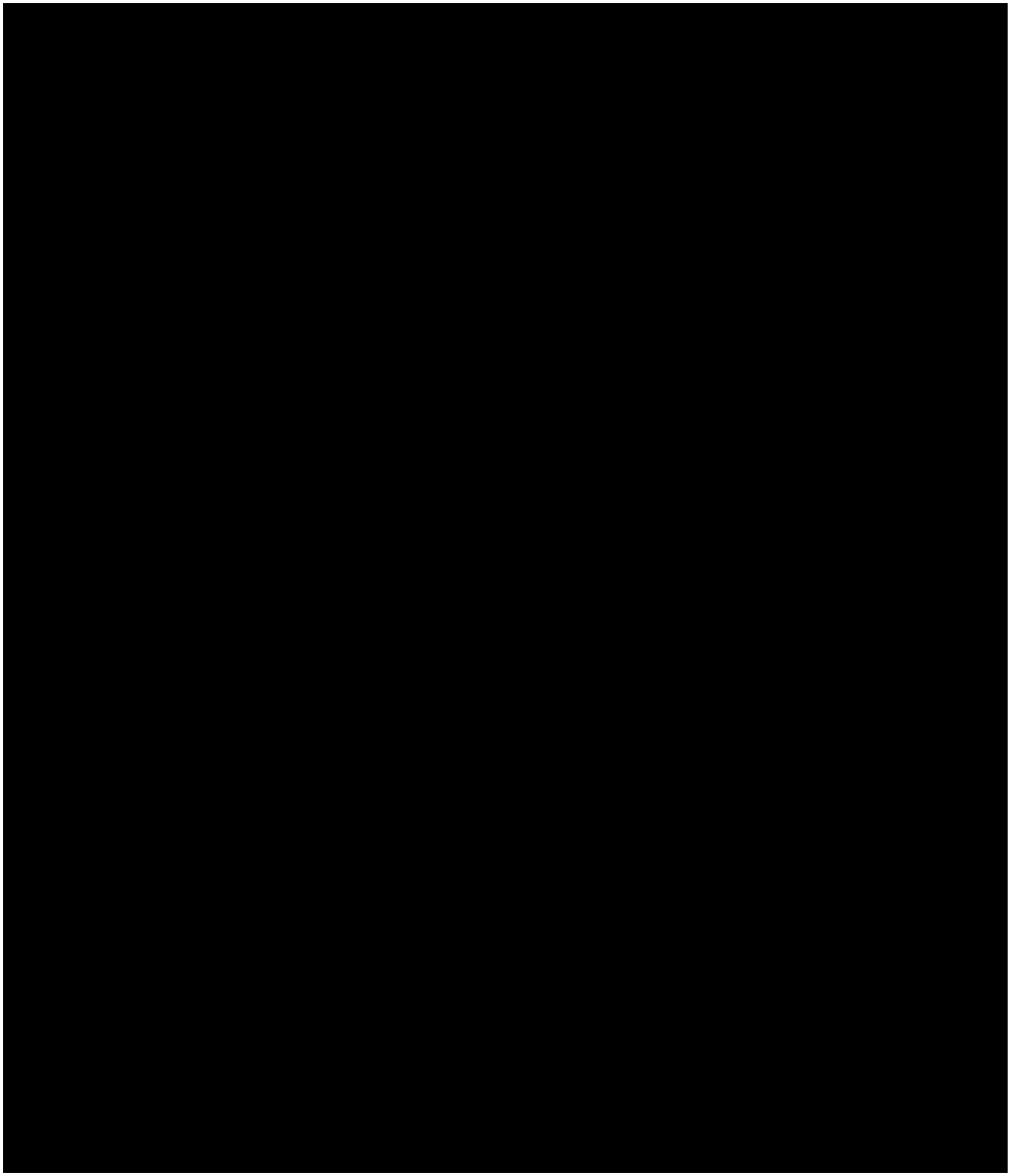
			NOTA-Aca-BBN PET/CT; the immunohistochemical staining confirmed a positive correlation between SUV and GRPR expression level. [25]

2.3.2 [^{68}Ga]-NeoBOMB1 in GRPR-positive malignancies

The [^{68}Ga]-NeoBOMB1 formulation, is currently under clinical investigation at the Innsbruck University, Austria. This is a Phase I/IIa study to evaluate safety, biodistribution, dosimetry and preliminary diagnostic performance of [^{68}Ga]-NeoBOMB1 in patients with advanced TKI-treated GIST using positron-emission tomography/computer tomography (PET/CT).

An additional objective is to improve the diagnostic accuracy in GIST via PET/CT, including tumours with TKI-resistant subtypes. Better detection capability, classification and definition of lesion extent are expected from the use of [^{68}Ga]-NeoBOMB1.

Following completion of the phase-I part of the study (6 patients completed), the product was shown to present a favorable safety and tolerability profile, with no adverse events (AEs) related with the compound (interim report released in November 2017). Uptake in tumour was fast with good imaging performance already at 1h after administration (Figure 1), associated with rapid renal and blood clearance.



The locally compounded [^{68}Ga]-NeoBOMB1 solution has been tested in the frame of a compassionate use program [redacted]. Twenty-four patients were administered with [^{68}Ga]-NeoBOMB1. No side effects have been reported and a good sensitivity was found compared to the conventional imaging. The results in four patients with prostate adenocarcinoma were reported by Nock et al. [7] .

The formulation tested in [redacted] is similar to the formulation developed by AAA: the drug substance is exactly the same, it's highly soluble and immediately bioavailable after

intravenous injection. It is also important to note that the final radiolabelled solution injected in patients is very similar for volume and pH in both cases, with the only exception of some excipients. The excipients used in the formulation developed by AAA (necessary to stabilize the product during lyophilisation, as well as to guarantee the long-term storage of the product) do not interact directly with the active substance and therefore do not have an impact on the disposition or clinical performance of the tracer.

2.4 Rationale and risks/benefits

The literature reports the GRPR overexpression in several malignant lesions but there is still a lack of precise data correlating GRPR overexpression to the molecular type of histological cancer as well as over the process of malignant transformation except for breast cancer [27]. In parallel, there are few studies focusing on GRPR imaging of primary tumours and metastatic lesions including lymph nodes. As there is a growing body of evidence suggesting that GRPR might be a valuable target for tumour identification and treatment, the Sponsor has conceived a study to investigate the diagnostic performance of NeoBOMB1, an antagonist with high affinity for GRPR, radioloabeled with a well-established PET isotope, Gallium-68 (^{68}Ga).

The Sponsor anticipates no biological effects of tracer dose (<50µg) of antagonist so no acute biological effects are expected. Regarding radioactivity, a dose of 3 MBq/kg ± 10% ranging within 150 to 250 MBq, is considered adequate to ensure appropriate imaging quality throughout the entire imaging protocol (latest time point at 4h p.i.) with ^{68}Ga as radionuclide. This dose-range is in line with the recommended activity to obtain a good quality image for other DOTA-conjugated peptides)[26]. The phase I/IIa study currently ongoing at Innsbruck University is injecting patients using the dose described above. Data coming from Innsbruck (interim safety and imaging report) shows that the administration of 50µg [^{68}Ga]-NeoBOMB1 in six patients diagnosed with GIST demonstrated good tolerability in all patients. No SAE was observed, and few minor side effects (fatigue, headache, lecocyturia, anemia) was observed in 2 patients with pre-existing conditions, with low probability to be causually related to the study drug administration. Pharmakokinetic analysis revealed a high in vivo stability and rapid renal excretion of [^{68}Ga]-NeoBOMB1 with highest accumulation in pancreas followed by kidney and liver. Overall these first clinical results shown both, a favourable safety profile and a preliminary good GRP-receptor targeting properties of [^{68}Ga]-NeoBOMB1, when administered at the standard gallium-68 low-radiation imaging dose. In terms of radioactive uptake kinetics, the interim report describes that following the administration of the compound there was a fast tumour-uptake, a rapid blood and renal clearance, which resulted in a good imaging performance as early as 60 minutes post-injection. In terms of dosimetry, the report describes a mean effective radiation dose of 0.026 mSv/MBq which is one-third lower than the calculated human-dose extrapolated from the animal model (0.039 mSv/MBq). With a maximum injected activity of 250 MBq the estimated effective dose would be 6.5 mSv per exam, which is lower that from the conventional [^{18}F]FDG-PET imaging.
The contribution of the low-dose CT is also to be contemplated. The amount of radiation dose from low-dose CT scan depends on different parameters, some related with the acquisition protocol (e.g. mA, mV), other intrinsic to the device used (e.g. single slice vs helical scanners). In the current protocol, to assess the pharmakcokinetic and the dosimetry of [^{68}Ga]-

NeoBOMB1, a maximum of 4 low-dose whole-body CT scans will be performed. An overall whole-body dose of maximum 7 mSv (from 4 to 7 mSv) per CT scan is expected.
For patients entering in the dosimetry group, a total theoretical radiation dose of 34,5 mSv is expected after administration of study drug plus the required four low-dose CT.. A total theoretical radiation dose of 20.5 mSv is expected for patients who will be included in the non-dosimetry group except for patients with PC who will receive an expected radiation dose of 27.5 mSv due to the additional CT scan required for them. In all the cases, the estimated effective dose will fall in the risk category level III as per the report 103 of the International Commission on Radiological Protection (ICRP) and are justified by a level of benefit as "Acquisition of knowledge, directly aimed at prevention or cure of serious disease". The standard radiation-exposure minimization measures including frequent bladder voiding is always a standard recommendation practice with radioligands presenting renal clearance, and is required in the current protocol. It is noteworthy reminding that this estimated total radiation dose is well aligned with the FDA recommendation of 30 mSv for adult research subjects receiving a single dose (Guidance for Industry and Researchers; "The Radioactive Drug Research Committee: Human Research without an Investigational New Drug Application", August 2010).

Another expected benefit of [^{68}Ga]-NeoBOMB1-PET relies on the potential early diagnostic detection of a recurrence, whether local relapse or distant metastasis, among those patients diagnosed with tumours expressing GRPR. Early and accurate detection translates in improved planning of treatment with classical therapeutic options, i.e. locoregional ablation techniques. Moreover, if [^{68}Ga]-NeoBOMB1 targets cancerous lesions with sufficient specificity and sensitivity, new treatment possibilities including peptide receptor radionuclide therapy may emerge.
In light of the disease status of the patients eligible for our study and the low risk of administration of [^{68}Ga]-NeoBOMB1, the benefit-risk balance is favourable and weights for patient's benefit.

3 Study design

3.1 Description of the study

Rationale of the design:
This is a Phase II, multi-center, open label, single dose study in cancer patients with tumour types known to overexpress GRPR, including breast, prostate, colorectal, small-cell and non-small cell lung.
The main objective of the Phase II study is the characterization of the preliminary targeting properties of [^{68}Ga]-NeoBOMB1 in patients with malignancies known to overexpress GRPR to assess the tumour-background ratio. The secondary objectives of the clinical trial are safety and tolerability and dosimetry aspects. All the objectives, with the exception of the secondary one relative to biodistribution and dosimetry that will be assessed 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 biodistribution 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 timepoints of the whole-body PET/CT scans for the remaining patients included in the non-dosimetry group will be adjusted.

Study conduct:

Population will be divided in two groups:

- **Phase-II dosimetry group**: 10 patients bearing breast and prostate cancer 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. Serial venous whole blood and urine samples will be collected for pharmacokinetic characterization. Patients will undergo a 15-min-static whole-body PET images at 15 min p.i.at 1h±15 min, 2h±15 min and 4h±30 min to determine absorbed doses to normal organs and to target tumour 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 from 0-2 h and from 2-4 h p.i. will also be collected.
- **Phase-II non-dosimetry group:** 40 patients will be enrolled in the second group. 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 tumour-types. Only prostate tumour 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.

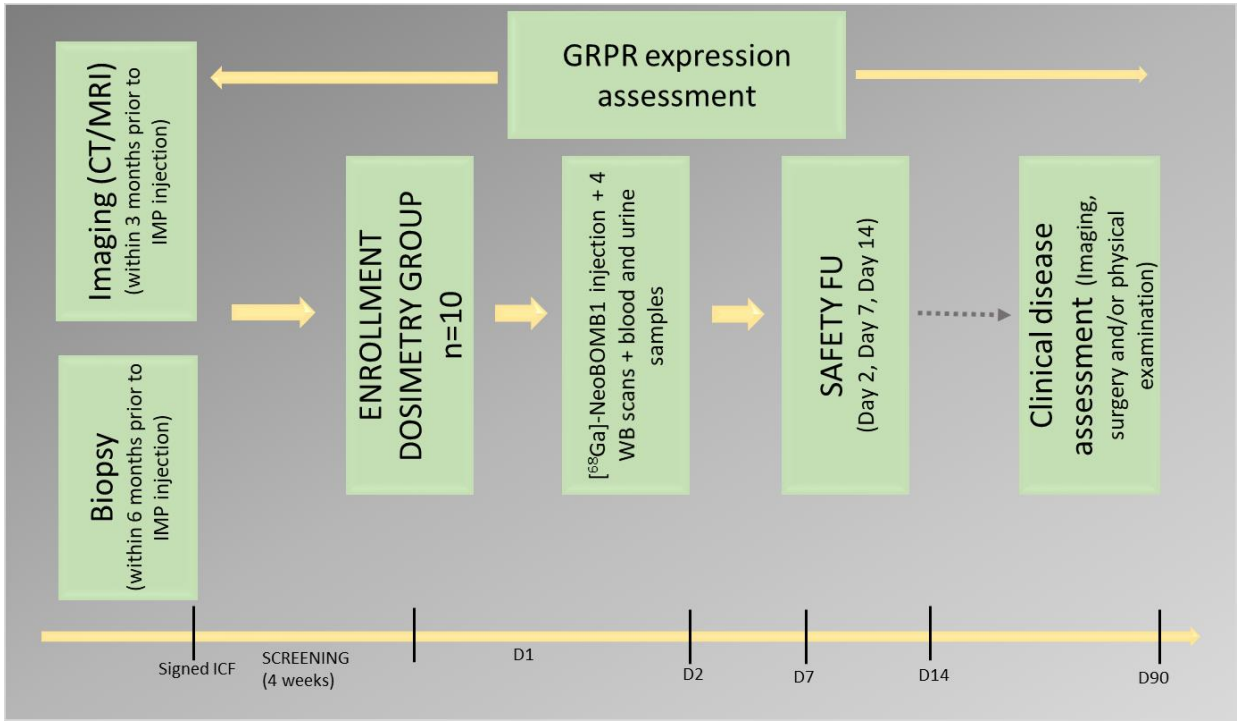


Figure 2: Overall study flow chart for dosimetry group

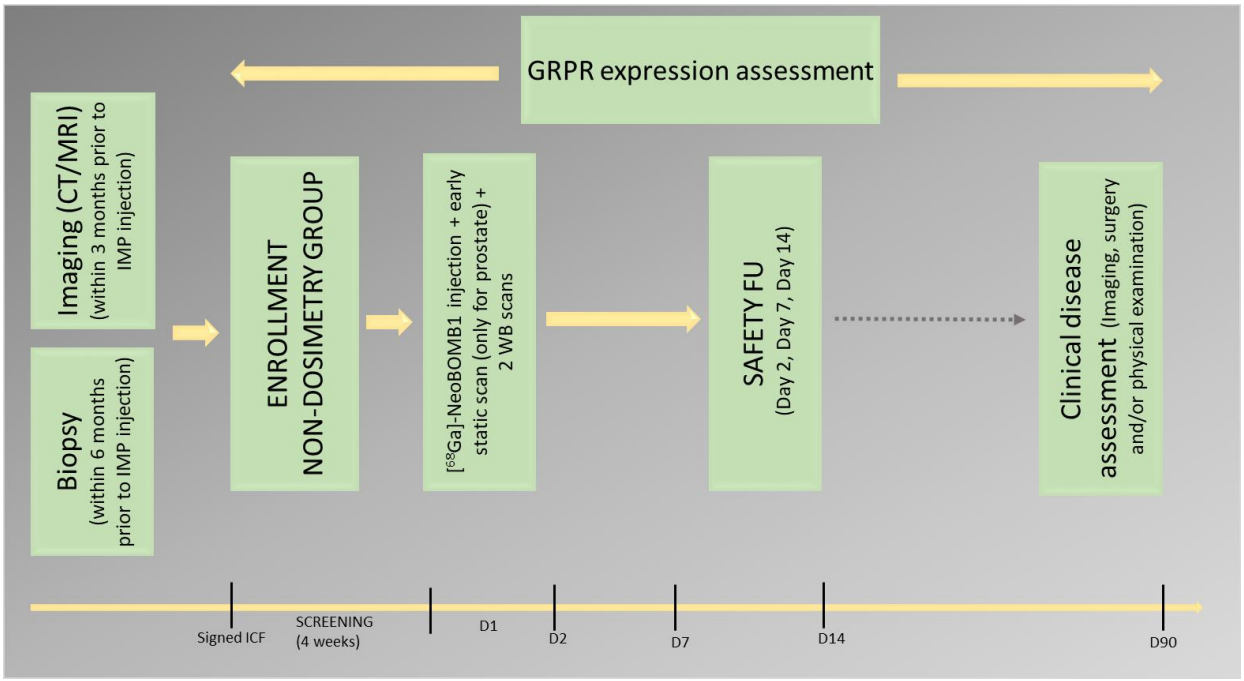


Figure 2bis: Overall study flow chart for non-dosimetry group

3.2 Study objectives

3.2.1 Primary Study Objective

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

3.2.2 Secondary Study 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 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]

3.3 Study Endpoints

3.3.1 Primary Study Endpoint

- Number and location of tumour lesions detected by [^{68}Ga]-NeoBOMB1 overall and for each tumour type
- Calculation of the ratio tumour/background SUV and calculation of percentage absorbed dose in tumour overall and for each tumour type.

3.3.2 Secondary Study Endpoints

- Standard safety parameters (clinical monitoring, laboratory, 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, ECG findings)
- Generation of decay corrected tissue TACs from [^{68}Ga]-NeoBOMB1 PET/CT images in normal organs, tumour 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, tumour lesions
- Calculation of residence times in organs and tumour lesions of [^{68}Ga]-NeoBOMB1
- Calculation of absorbed doses and effective whole body dose of [^{68}Ga]-NeoBOMB1
- Calculation of the SUV of each lesion
- Number and location of tumour 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 tumour type
- Comparison of number of patients with tumour lesions detected and number of tumour 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]

3.4 Study population / Selection of subjects

3.4.1 Inclusion criteria

1. Subjects must be at least 18 years of age
2. Subjects must have signed and dated an informed consent prior to any study-specific procedures.
3. Subjects with histologically-confirmed tumour, for whom a recent biopsy (not older than 6-month-old) has been performed.
4. Dosimetry group:
    - Luminal breast cancer
    - Adenocarcinoma of the prostate
5. Non-dosimetry group:
    - Luminal breast cancer
    - Adenocarcinoma of the prostate
    - Small cell lung cancer
    - Non-small cell lung cancer
    - Colorectal carcinoma
6. At least one malignant lesion detected *via* functional or morphological imaging (PET combined to appropriate tracer according to tumour type (PET combined to appropriate tracer according to tumour type, CT, MRI) within 3 months prior to [^{68}Ga]-NeoBOMB1 administration.
7. The Eastern Cooperative Oncology (ECOG) performance status 0-2.
8. Subjects must agree to use highly effective methods of contraception (female partners of male participants should use highly effective methods of contraception) during the trial.

3.4.2 Exclusion criteria

1. Renal insufficiency or an eGFR <50 ml/min/1.73m^2.
2. Haematological toxicity grade > 2 (Toxicity Grading Scale in vaccine clinical trials)
3. Participation in any other investigational trial within 30 days of study entry.
4. Subjects with positive pregnancy test (Urine dipstick), and/or currently breast-feeding
5. Concurrent severe illness or clinically relevant trauma within 2 weeks before the administration of the investigational product that might preclude study completion or interfere with study results.
6. Concurrent bladder outflow obstruction or unmanageable urinary incontinence.
7. Known or expected hypersensitivity to [^{68}Ga]-NeoBOMB1, or any excipient present in [^{68}Ga]-NeoBOMB1.
8. Any condition that precludes raised arms position
9. Prior administration of a radiopharmaceutical within a period corresponding to 8 half-lives of the radionuclide.
10. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.

3.4.3 Patients recruitment

Recruitment of subjects is center competitive, i.e. there is no maximum recruitment per center, rather all centers will stop recruiting when the 50th subject is undergoing [^{68}Ga]-NeoBOMB1-PET.

To accurately answer the primary objective, recruitment of subjects requires that each of the 5 tumour types be equally represented. Therefore, 5 subgroups accounting with 10 subjects bearing the same tumour type will be formed.

The **dosimetry group** will be formed by 5 patients with breast cancer and 5 patients prostate cancer. Patients will decide by themselves whether they want to participate in the dosimetry or the non-dosimetry group.

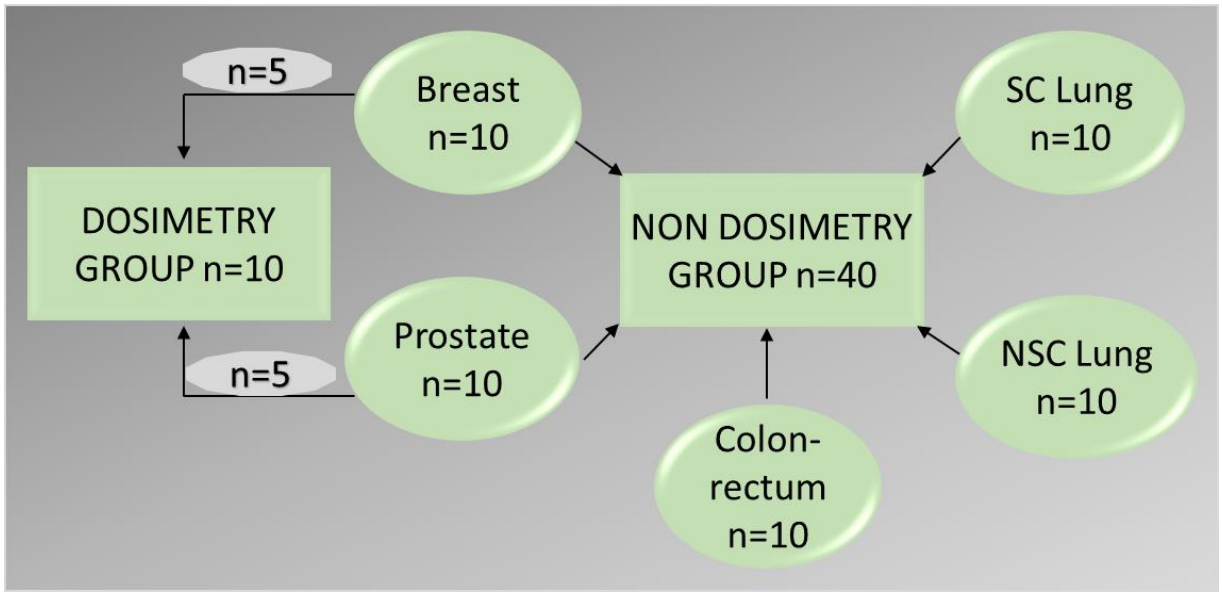


Figure 3: Patients' recruitment chart

3.4.4 Patient ID definition

A unique subject identification number will be assigned at the start of the screening period to each subject who signs the informed consent form. This number will identify the subject throughout the study and ensure the identity confidentiality of the subject.

Subject identification numbers will include a 2-letter country code, a 2-digit site code and a 3-digit subject number (ex: [redacted] for the first recruited patient at site [redacted] in France).
Kits will be allocated for single subject use.

3.4.5 Withdrawal of trial subjects after trial start

Reasons for removal investigational treatment or observation might include:

- Withdrawal of consent
- Pregnancy
- Significant protocol deviation
- Subject non-compliance
- Adverse event
- Other safety concern of the investigator or sponsor
- Death
- Lost to follow-up

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.
Withdrawal of consent for the study means that the subject does not wish to receive further investigational treatment and does not wish or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the subject's study data, but no further information will be collected.
For any patient who has received Investigational Medicinal Product (IMP) and withdrew prematurely from the study every effort should be made for attendance of a safety follow-up visit. The primary reason for withdrawal from the study should be documented. Patients will not be followed for any reason after consent has been withdrawn.
The investigator has the right to discontinue a patient from IMP or withdraw a patient from the study at any time. The primary reason for withdrawal from the study should be documented.
If a patient discontinues the study participation after administration of [^{68}Ga]-NeoBOMB1 and generation of all measurements for reasons unrelated to an adverse event and does not object to the use of the generated data, the data will be used. If a patient discontinues the study participation before administration of [^{68}Ga]-NeoBOMB1, the patient will be replaced by another patient. However, if the withdrawal is after the administration, the patient will not be replaced.

3.4.6 Closure of trial sites/Premature termination of the clinical trial

3.4.6.1 Premature termination of trial

The sponsor has the right to terminate the trial prematurely at any time.
This might be if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination, which must be documented.
Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly
- It is no longer ethical to continue application of [^{68}Ga]-NeoBOMB1
- The sponsor considers that the trial must be discontinued for safety reasons
- It is no longer practicable to complete the trial

The sponsor decides on whether to discontinue the trial in consultation with the PI.
In case of discontinuation of the trial, the EC and Competent Authority (CA) must be informed within 15 days of early termination.

4 Study procedures and schedule of assessments

4.1 Study procedures

4.1.1 Informed consent form

It is the responsibility of the PI, or a person delegated by the PI to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.
The PI or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.
No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrollment into the trial.
A copy of the signed Informed Consent Form (ICF) will be given to the participant. The original signed and dated form will be retained at the study site.
If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

4.1.2 Physical examinations

Physical examinations will be performed at all visits except at Day 2 for patients included in the non-dosimetry group. All of them will be performed by trained medical personnel only, prior to IMP administration on the dosing day. Any abnormal findings will be recorded as AEs. Furthermore, auscultation of lungs and heart and palpation of abdomen will be performed

4.1.3 Vital signs

Vital signs will be measured at all visits except at Day 2 for patients included in the non-dosimetry group.

On injection/PET day, i.e. Day 1, vital signs will be recorded

- at pre-dose, immediately after radiotracer injection, 30 min p.i. and after the last image acquisition (about 4h) among patients of the **dosimetry group.**
- at pre-dose, 30 min p.i. among patients of the **non-dosimetry group.**

Heart rate and blood pressure will be measured after patient has been in a seating position for 5 minutes.

4.1.4 ECG

A standard 12-lead ECG assessment will be performed at all visits except at Day 2 for patients included in the non-dosimetry group. The following parameters must be recorded: RR, PR, QRS, and a more extended QT-time (QTc) evaluation according to ICH E14, and heart rate.
On injection/PET day, i.e. Day 1, ECG will be recorded

- at pre-dose, immediately after radiotracer injection, 30 min p.i. and after the last image acquisition (about 4h) among patients of the **dosimetry group.**
- at pre-dose, and 30 min p.i. among patients of the **non-dosimetry group.**

ECGs for each patient will be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a rest position for > 5 minutes prior to ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital signs measurements and blood draws.
For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings.

4.1.5 Routine laboratory exams and pregnancy test

Routine laboratory exams will be performed at all visits except at Day 2 for patients included in the non-dosimetry group.
Clinical Laboratory:
Blood chemistry: Non-fasting glucose, Urea, Creatinin, eGFR (calculated), Bilirubin, Na, K, Cl, Ca, GOT (ASAT), GPT (ALAT), γGT, ALP, pancreatic amylase, pancreatic lipase, LDH, CK, CRP, albumin
Haematology: Haemoglobin, haematocrit, RBC count, absolute WBC count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelets
Coagulation parameters: Quick, INR, aPTT, fibrinogen
Pregnancy test (in women of childbearing potential): dip-stick
Urinalysis *via* dip-stick: appearance, colour, pH, protein, glucose, blood

The total volume of blood required per patient for standard clinical laboratory assessments will be approximately 16.5 mL for 3 full tubes on each sampling occasion.

Among patients of the **dosimetry group**, routine laboratory exams will be performed at Screening, Day 1, Day 2, Day 7±1 and Day 14±2. In addition, 1 mL of venous whole blood per time-point will be drawn for the biodistribution assessment at Day 1. A total volume of 90.5 mL venous blood will be withdrawn.

Among patients of the **non-dosimetry group**, routine laboratory exams will be performed at Screening, Day 1, Day 7±1 and Day 14±2 for a total volume of withdrawn venous blood of 66 mL.

4.1.6 Imaging

[^{68}Ga]-NeoBOMB1 imaging will be performed using a standard integrated PET/CT system. All imaging will be performed at the Department of Nuclear Medicine.

It is important to remember to record the patients' weight and height in the PET system software.
The patient must be hydrated per os with at least 750 mL of bottled drinking water 1 h before of image acquisition.
A standard PET/CT tomograph consists of a LSO PET system combined with a multi-row spiral CT system.
Immediately before the PET/CT examination, patients are requested to empty their bladder. Patients are positioned supine with raised arms and head-first on the common patient handling system in accordance with standard CT practice.
First, a topogram will be acquired over 1,024 mm axially. Coaxial whole-body imaging ranges will be defined on the topogram, covering an area from the skull to the mid-thighs (6-7 PET bed positions, or 90–110 cm, depending on the size of the patient). CT shall be performed for attenuation correction purposes and anatomical reference for subsequent PET acquisition. During the CT acquisition a limited breath hold protocol will be followed, which required the patients to hold their breath in normal expiration. After completion of the CT, patient's bed moves automatically to the PET gantry, where 3D PET emission scanning subsequently will starts in the caudocranial direction.

The administration of the radiotracer will be performed using a venous access, injection volume will be up to 5.5 ml with a slow bolus paradigm however conserving the same procedure time for all the patients. During this slow bolus, vital signs will be monitored. The radiolabeling protocol ensures that standard conditions are kept in terms of peptide mass.
In case of SAEs, the injection will be stopped immediately and reported based on the Toxicity Grading Scale in vaccine clinical trials.

Patients of the dosimetry group will undergo 4 sequential PET/CT scans. The IMP [^{68}Ga]-NeoBOMB1 injection should occur prior to the start of any imaging. Patients should be positioned and imaging should begin at 15min, 1h±15min, 2h±15min and 4h±30min post IMP injection with PET/CT scans consisting of low dose attenuation correction CT scans followed by PET images acquired from the head through the mid-thigh (approximately 6-7 beds

depending on patient height). PET data will be corrected for photon attenuation, dead-time, random events and scatter.

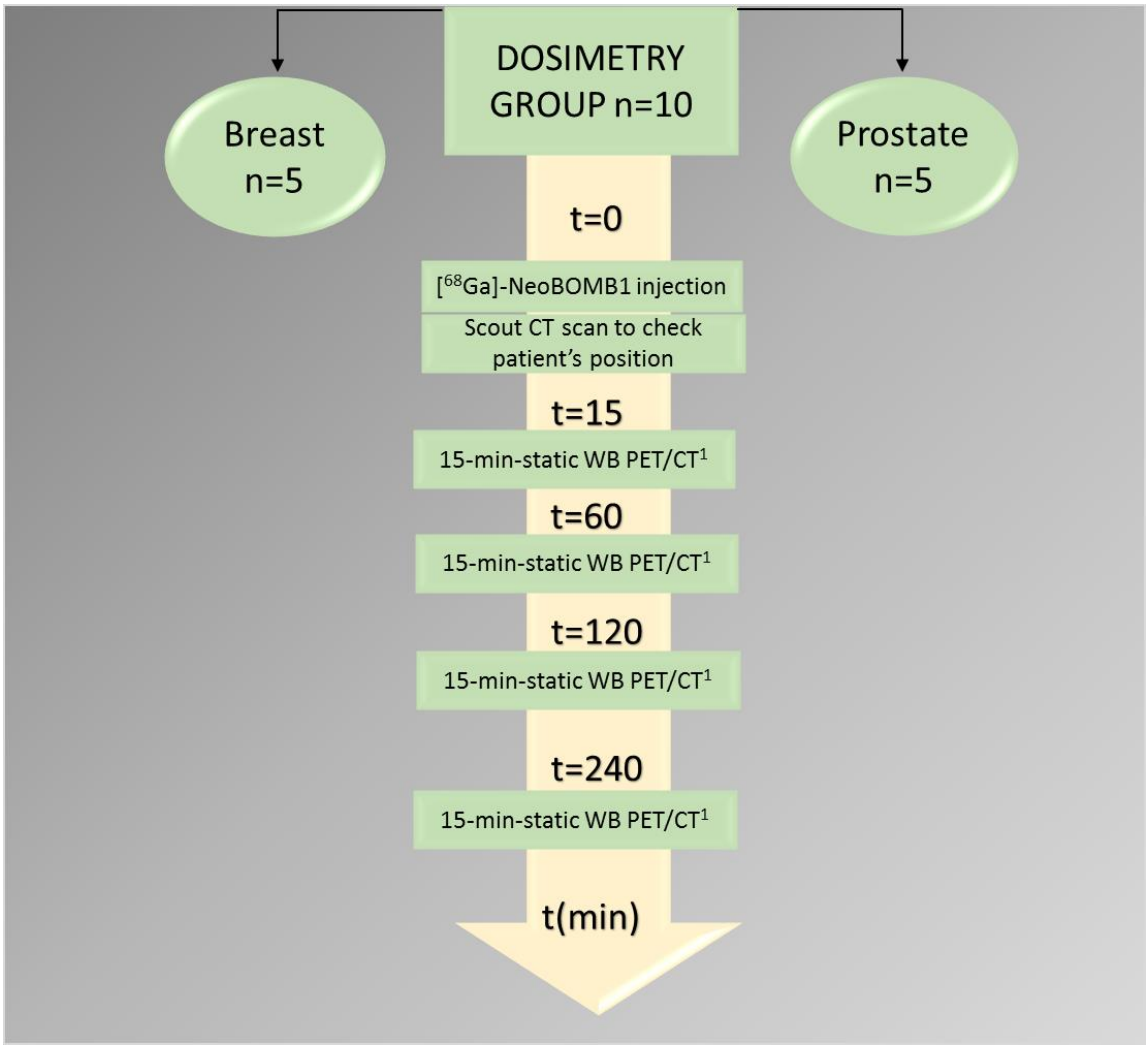


Figure 4: Dosimetry group PET imaging flow chart

[1]WB PET/CT : low-dose for 4 WB PET/CT from the vertex to the upper thighs for attenuation correction followed by a total-body PET examination

Affinity parameters of the [^{68}Ga]-NeoBOMB1 (KD) will be used to create a model able to predict dose to tumour and relevant organs (pancreas, kidney, liver) expected to present the greatest relative tracer uptake when a bombesin antagonist (such as [^{68}Ga]-NeoBOMB1) is administered.
The images will be analysed with regards to the diagnostic suitability of [^{68}Ga]-NeoBOMB1 for tumour targeting as well as the safety of the procedure (whole body dosimetry of [^{68}Ga]-NeoBOMB1).

Patients of the **non-dosimetry group** will undergo 2 whole-body PET/CT scans at 90±30min and at 150±30 min. Patients with prostate cancer will also undergo a 5-min static PET/CT scan on relevant regions for lymph node imaging purpose (if applicable).

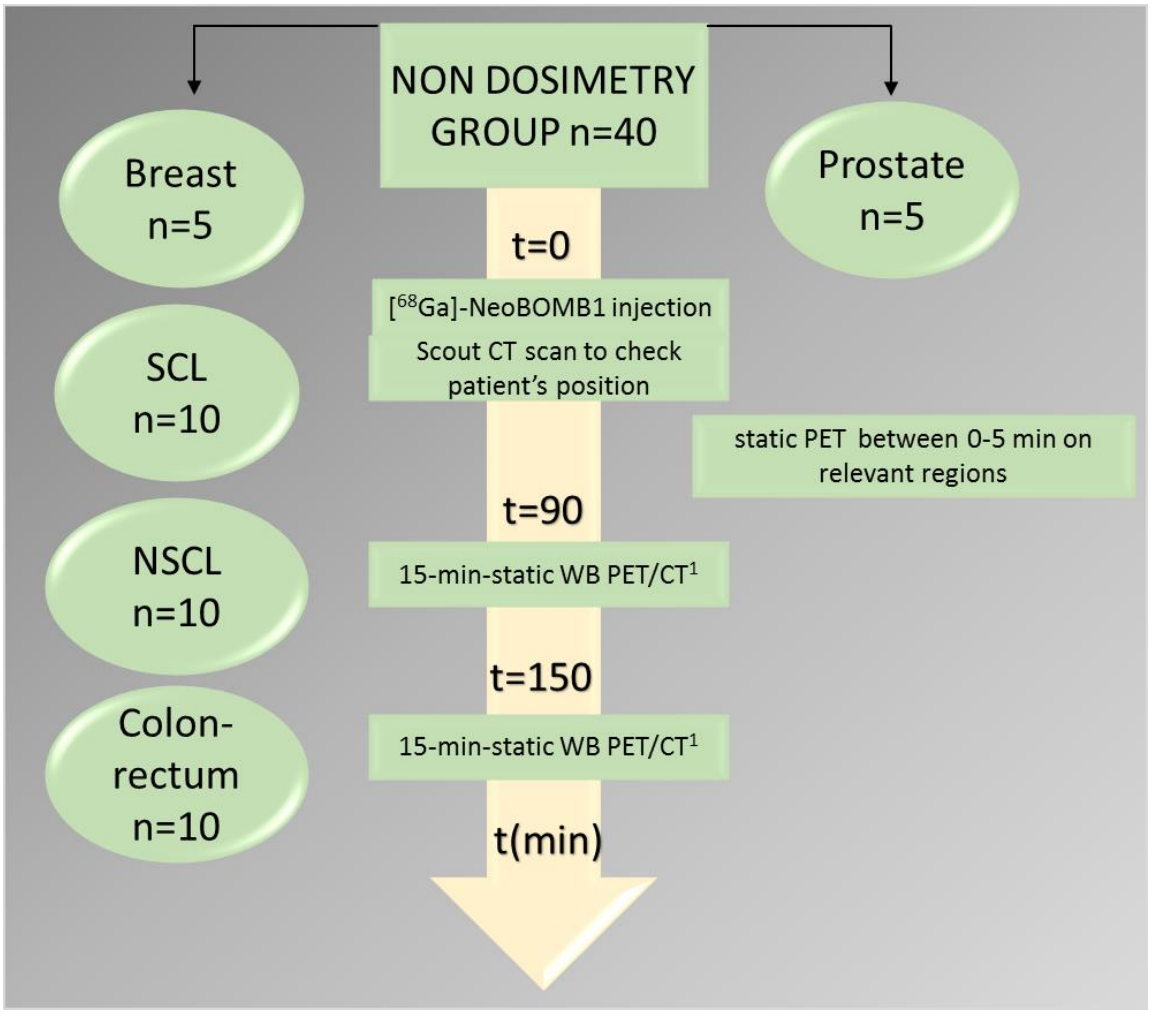


Figure 5: Non-dosimetry group PET imaging flow chart

[1]WB PET/CT: low-dose from the vertex to the upper thighs for attenuation correction followed by a total-body PET examination

Data Reconstruction and Image Analysis

The CT transmission images are used for attenuation correction of the PET emission data. After scatter and attenuation correction, PET emission data must be reconstructed using an attenuation-weighted ordered-subsets maximization expectation approach with 2 iterations and 8 subsets on 128x128 matrices and with a 5-mm Gaussian post-reconstruction filtering.

Semi-quantitative analysis (SUV_{max} and mean) per tumour type group and time point will be conducted to establish pathological thresholds or pathological/physiological ratio thresholds and determine [^{68}Ga]-NeoBOMB1-PET diagnostic performance.
Similarly, organs receiving the highest organ dose (HT) will be identified and radiation doses per organ (µGy/MBq) as well as effective organ doses (µSv/MBq) will be computed.

PET data will be transferred to the central imaging center in an anonymized way to protect patient's privacy. A procedure is detailed in a separate central imaging reading center manual provided to each site. Briefly, for data transfer, 4 types of files are generally used: Excel info

file, Excel biokinetic PET/CT data, PET/CT DICOM files and additional files (containing the data of the other tests).
The Excel info file shall include all procedures performed in every patient and relative demographic (age, weight, height, etc.) as well as the Patient's ID.
The Excel biokinetics file shall include all PET/CT non-imaging data (activity data) for the different time points (according to the PET/CT protocol) for every measured organ as well as the measured volumes for each organ in every patient. This information will be transferred as an MS Excel file (for processing) and as printed documents signed by the person in charge (for verification and control).
The DICOM files will contain the anonymized raw PET/CT data (using the internal Patient IDs) plus RT structure DICOM files for the structures drawn for the organs at risk (ROIs).
The additional files consist of the additional tests performed on the patients such as hemograms, semi-quantitative urine analyses and organ volume measurements. This information is to be also anonymized and renamed with the assigned internal Patient IDs. This information will be sent in digital form as well as printed documents (for verification and control).
All the electronic information (DICOM files, MS Excel files and PDF files) will be stored on DVDs (original and backup copy in case of having any trouble with the original one).

All other relevant info relative to patients must be sent to the central reading center, including the standard morphologic imaging study that has detected the malignancy or its recurrence, likely to be CT, MRI or PET, in DICOM format, with the same anonymization method used for the internal Patient IDs. An excel file will include specific info about such study, the date of acquisition, the protocol used, the injected tracer if pertinent, the scan duration, the reconstruction algorithm as well as the medical interpretation from the radiologist/nuclear medicine physician.

4.1.7 Biodistribution and dosimetry

Sequential venous blood samples of 1 mL at baseline (immediately prior to injection, time 0) and at 5, 10, 20, 30±5, 1h±5min, 2h±10min and 3-4h±10min as well as 1ml-urine samples from the one produced over 0-2h and 2-4h after the end of infusion for dosimetric measurements will be collected.
Dosimetry calculations will be issued from the analyses of organs receiving the highest dose, identified visually. ROIs/VOIs will be placed over these organs to determine relative radiotracer uptake calculated as a percentage of the injected dose per gram of tissue (%ID/g). Tissue activity curves 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 ACs 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.

4.1.8 Assessment of GRPR expression

Assessment of GRPR expression must be assessed while the study is ongoing within 4 weeks after IMP injection. GRPR expression is analyzed by a single central laboratory to ensure homogeneity of procedures. The technique used by the central laboratory together with the requirements of preparation of the tissue samples is detailed in a separate laboratory manual provided to each study site. Briefly, a surgery/biopsy specimen of the malignant lesion sampled 6 months prior to IMP injection at the earliest will be assessed by immunohistochemical staining.

4.1.9 Adverse Events and Concomitant Medications

Adverse events and concomitant medications will be reported and recorded from the signature of the (ICF) until the end of the study (Section 6 of the protocol).

4.2 Schedule of assessments

4.2.1 Screening period (Visit 0, days –28 to – 1)

The screening examinations must be performed between 1 and 28 days before being enrolled in the study (i.e. administration of [^{68}Ga]-NeoBOMB1). Only subjects fulfilling all the inclusion and none of the exclusion criteria will be accepted in the study.
The following study screening assessments are to be completed within 1 to 28 days prior to study entry:

- Signed and dated informed consent
- Reviewed inclusion and exclusion criteria
- Demographic data: age and sex
- Medical history: relevant prior or persisting illnesses including known allergies, prior anaphylactic reactions, metabolic disorders, vascular disorders, hypertension, history of stroke or myocardial infarction, other known malignancies, prior treatment
- Concomitant medication
- Physical examination: weight, auscultation of lungs and heart, oral inspection, abdominal palpation
- Vital signs: blood pressure, heart rate
- Routine ECG including frequency-corrected QT-time
- Haematology, Blood chemistry, Coagulation parameters, Urinalysis
- Urine dipstick pregnancy test (in women of childbearing potential)

4.2.2 Injection/PET Imaging day (Day 1/Visit 1)

Before administration

Hospitalization will occur on the day of administration of [^{68}Ga]-NeoBOMB1.
For all patients, the following study assessments will be performed on the day of administration of [^{68}Ga]-NeoBOMB1:

- Participant will be asked to drink 750 ml of water within 1h before image acquisitions
- Control of dated informed consent
- Review of inclusion and exclusion criteria
- Control of adverse events and concomitant medications
- Physical examination: weight, auscultation of lungs and heart, oral inspection, abdominal palpation
- Vital signs: blood pressure, heart rate
- 12-lead ECG including frequency-corrected QT-time
- Haematology, Blood chemistry, Coagulation parameters: Quick, INR, aPTT, fibrinogen, Urinalysis
- Urine dipstick pregnancy test (in women of childbearing potential)
- Venous blood sampling (~1 ml) for radioactivity assay (only for dosimetry group)
- Urine collection for radioactivity assay (only for dosimetry group)
- Histopathologic evaluation
- Concomitant medications can be administered from 4h after the [^{68}Ga]-NeoBOMB1 administration.

During and after administration

For patients included in the **dosimetry group**, the following safety assessments will take place:

- Vital signs: blood pressure, heart rate immediately after administration of [^{68}Ga]-NeoBOMB1, at 30 min after administration and after the last whole-body scan (around 4 h)
- Routine ECG including frequency-corrected QT-time immediately after administration of [^{68}Ga]-NeoBOMB1, at 30 min after administration and after the last whole body scan (around 4 h)
- Venous whole blood sampling (~1 ml) for radioactivity assay at 5, 10, 20, 30±5min, 60±5 min and 2h±10 min and 3-4h±10 min.
- Urine collection for radioactivity assay (~1 ml) from 0-2h and from 2-4h. In addition, the subjects will be requested to void immediately.
- Static whole-body PET at 15min, 1h±15 min, at 2h±15 min and at 4h±30 min.

For patients of the **non-dosimetry group**, the following safety assessments will take place:

- Vital signs: blood pressure, heart rate 30 min p.i.
- Routine ECG including frequency-corrected QT-time 30 min p.i.
- Static PET scan between 0 and 5 min only for the prostate subgroup (if applicable)

- Static whole-body PET at 1h30±30 min and at 2h30±30 min

4.3 Safety follow-up visits (Day 2/Visit 2, Day 7/Visit 3 and Day 14/Visit 4)

Patients will be discharged on the day 1 after administration of [^{68}Ga]-NeoBOMB1 in case of no or minor adverse events that do not contradict such a discharge.
FU visits are scheduled 1 day (Visit 2), 7±1 days (Visit 3) and 14±2 days (Visit 4) after administration of [^{68}Ga]-NeoBOMB1 and will encompass:

- Physical exam,
- Vital signs,
- 12-lead ECG
- Blood sampling to determine haematological and biochemical parameters,
- Dipstick test for urinalysis
- Check-up of concomitant medication,
- Assessment for adverse events.

On Day 2, patients included in the **non-dosimetry group** will receive a FU phone call to assess any potential adverse events, allergic reactions and concomitant treatments. For this group of patients, Day 7±1 is an optional FU physical visit and can be replaced by a phone call to assess any potential adverse events, allergic reactions and concomitant treatments.

4.4 Optional routine clinical disease follow-up

If available, within 3 months from IMP injection, data generated from the routine clinical follow-up of the patients in the frame of routine patients' management will be collected to help with the interpretation of previous focal uptake of [^{68}Ga]-NeoBOMB1 PET which was not corresponded to detectable morphological lesions on CT/MRI

4.5 Visit and Assessment Schedule

Phase II dosimetry group:

Time point		**Visit 0 Screening**	**Visit 1 PET Imaging Day**								**Visit 2 FU**	**Visit 3 FU**	**Visit 4 FU**	**Optional routine clinical disease FU[7]**
Examination/Evaluation	**Day**	**-28 to -1**	**1**								**2**	**7±1**	**14 ±2**	**Max 90**
	HH:mm		Pre-dose	0-5 min	5-15 min	20 min	30 min	1h	2h	3-4h				
Informed Consent		●												
Inclusion / Exclusion criteria[1]		●												
General														
Demographic Data		●												
Medical History		●	●											
Physical Exam		●	●								●	●	●	
Vital Signs		●	●	●			●			●	●	●	●	
Blood analysis (hemato, biochemistry, coagulation)		●	●								●	●	●	
Urine analysis[2]		●	●								●	●	●	
Pregnancy Test[3]		●	●											
12-lead ECG		●	●	●			●			●	●	●	●	
Concomitant Medications		●	●								●	●	●	●
Baseline findings / Adverse Events		●	●								●	●	●	●
IMP Administration & Dosimetry														
[^{68}Ga]-NeoBOMB1 Injection				●										
Blood sampling / radioactivity[4]			●	●	●	●	●	●	●	●				
Urine collection / radioactivity[5]			●	●			●							
[^{68}Ga]-NeoBOMB1 PET/CT imaging														
Static, whole Body[6]					●			●	●	●				
GRPR expression assessment[8]		●												

1. Standard conventional imaging required
2. Urine dipstick test
3. Negative urine pregnancy test at Baseline and within 24 hours prior to administration.
4. Time-points: pre-injection, 5, 10, 20, 30±5, and 1h±5min, 2h±10min, 3-4h±10min post-injection
5. Time-points: pre-injection, from 0-2h and from 2-4h post-injection
6. WB PET/CT: low-dose CT, non-enhanced CT from the vertex to the upper thighs for attenuation correction followed by a total-body PET examination

7. Any relevant data generated from the routine clinical disease follow-up will be collected: CT/MRI, biopsy, physical examination
8. GRPR expression assessment must be performed within 4 weeks after IMP injection

Phase II non-dosimetry group:

Time point		**Visit 0 Screening**		**Visit 1 PET Imaging Day**				**Visit 2 FU[4]**	**Visit 3 FU[5]**	**Visit 4 FU**	**Optional routine clinical disease FU[7]**
Examination/Evaluation	**Day**	**-28 to -1**		**1**				**2**	**7±1**	**14±2**	**Max 90**
	HH:MM		Pre-dose	0-5 min	30 min	1h30±30min	2h30 ± 30 min				
Informed Consent		●									
Inclusion / Exclusion criteria[1]		●									
General											
Demographic Data		●									
Medical History		●	●								
Physical Exam		●	●						●	●	
Vital Signs		●	●	●	●				●	●	
Blood analysis (hemato, biochemistry, coagulation)		●	●						●	●	
Urine analysis[2]		●	●						●	●	
Pregnancy Test[3]		●	●								
12-lead ECG		●	●	●	●				●	●	
Concomitant Medications		●	●					●	●	●	●
Baseline findings / Adverse Events		●		●				●	●	●	●
IMP Administration											
[^{68}Ga]-NeoBOMB1 Injection				●							
[^{68}Ga]-NeoBOMB1 PET/CT imaging											
Static scan (prostate cancer –if applicable)				●							
Static, whole-body[6]						●	●				
GRPR expression assessment[8]			●								

1. Standard conventional imaging required
2. Urine dipstick test
3. Negative urine pregnancy test at Baseline and within 24 hours prior to administration.
4. Phone call

5. Visit or phone call
6. WB PET/CT: low-dose for 4 WB PET/CT from the vertex to the upper thighs for attenuation correction followed by a total-body PET examination
7. Any relevant data generated from the routine clinical disease follow-up will be collected: CT/MRI, biopsy, physical examination
8. GRPR expression assessment must be performed within 4 weeks after IMP injection

5 Study medication

5.1 Name and description of Investigational Medicinal Product

The name and pharmaceutical form of the IMP is [^{68}Ga]-NeoBOMB1 kit for radiopharmaceutical preparation.

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

- Vial 1: NeoBOMB1, 50 µg, powder for solution for injection, to be reconstituted with a solution of gallium-68 chloride ($^{68}GaCl_3$) in HCl eluted from a ^{68}Ge/^{68}Ga generator;
- Vial 2: Reaction buffer. Vial 2 is to be added to the reconstituted Vial 1.

The kit has to be used in combination with a solution of 68Ga in HCl provided by a 68Ge/68Ga generator to obtain ^{68}Ga-NeoBOMB1 solution for injection, being the Radiolabelled Imaging Product, which can be directly injected to the patient.

The volume of ^{68}Ga-NeoBOMB1 solution for injection, corresponding to the radioactive dose to be administered, is calculated according to the estimated time of injection, on the basis of the current activity provided by the generator and of physical decay of the radionuclide (half-life = 68 min).

It is a mono-dose product.

Vial 1 is a powder for solution for injection containing 50 µg NeoBOMB1 as active ingredient.

The powder is packed in 10 mL Ultra inert Type I Plus glass vials.

Vial 2 Reaction buffer contains no active ingredient.

Reaction buffer solution is contained in a 10 mL cyclic olefin polymer vial.

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

5.2 IMP administration

[^{68}Ga]-NeoBOMB1 must be prepared and administered at the investigational site by appropriately trained personnel.
The lyophilized vial 1 (containing the NeoBOMB1 peptide) shall be directly reconstituted with the ^{68}GaCl solution in ultrapure HCl provided by a ^{68}Ge/^{68}Ga generator. After addition of the suitable volume of reaction buffer (vial 2) and heating at 95°C for 7 minutes, the ^{68}Ga-labelled product is ready to use.
^{68}Ga eluate should be obtained from an approved commercial ^{68}Ge/^{68}Ga generator that has been eluted within the past 4 hrs.

The recommended activity to be administered is 3 MBq/Kg (± 10%), but not more than 250 and not less than 150 MBq.
Refer to Appendix 1 for instruction on the radiolabelling procedure and dispensing [^{68}Ga]-NeoBOMB1, cautionary notes, analytical controls and stability of the radiolabelled product.

5.3 Dose modifications

Not applicable

5.4 Concomitant medication

Patients can be under active systemic treatment such as anti-cancer therapy or hormonal therapy. However, the IP administration should be done at least 72 hours after administration of chemotherapy, to allow for the resolution of any acute side effects. Chemotherapy administration or the start of a new anti-cancer therapy should also be held until 48hrs after IP administration.

Regional/local radiation should be completed at least 2 weeks before administration of IP. Focal radiation therapy is allowed after discussion with the study medical monitor.

The participation of patients on treatment with check-point inhibitors should be discussed with the study medical monitor, to assess concurrent adverse events and side effects prior to administration.
Any other allowed concomitant prescribed medications should be discontinued 2h before and until 4h after administration of [^{68}Ga]-NeoBOMB1.

5.5 Labelling

Primary and Secondary packaging for the IMP will be prepared according to Annex 13 of GMP (Good Manufacturing Practice) European directive (Eudralex Volume 4), The information that will be included in the final labels are reported in the examples below in English.
As per guidelines, labels of the primary and secondary packaging will be translated in the investigational site local language.

Primary Packaging (powder and buffer vial):

NeoBOMB1 Powder vial
For clinical trial use only. Intravenous use after radiolabelling
Powder for radiopharmaceutical preparation of 68Ga-NeoBOMB1
One vial of powder containing 50µg of NeoBOMB1.
EXP: mm/yyyy Lot: xxx
Store in a refrigerator
EudraCT number: 2017-003432-37 Patient Number: xxx
Sponsor: **Manufacturer:**
Advanced Accelerator Applications International S.A.
[redacted] ITALY

Buffer vial
For clinical trial use only
Reaction buffer solution for radiopharmaceutical preparation of 68Ga-NeoBOMB1. Intravenous use after radiolabelling
EXP: mm/yyyy Lot: xxx
Store in a refrigerator
EudraCT number: 2017-003432-37 Patient Number: xxx
Sponsor: **Manufacturer:**
Advanced Accelerator Applications International S.A.
[redacted] ITALY

Secondary Packaging (outer box)

NeoBOMB1 50 µg, kit for the radiopharmaceutical preparation
For clinical trial use only
Intravenous use after radiolabelling. For single use.
Refer to the study protocol for directions for use
One vial of powder contains 50µg of NeoBOMB1.
EXP: mm/yyyy Lot: xxx
Store in a refrigerator.
After radiolabelling, store below 25°C
EudraCT number: 2017-003432-37 Patient Number: xxx
Sponsor: **Manufacturer:**
Advanced Accelerator Applications International S.A.
Investigator: xxx
[redacted] Italy

5.6 Handling and storage of IMP at the Site and IMP Accountability

The kit for the preparation of [^{68}Ga]-NeoBOMB1 should be stored upon receipt at 5°C ± 3°C in a temperature-controlled refrigerator.
Regulation on how medication labelled with „For clinical trial use only" is managed:

- Dispensary on pharmacy/investigator (if applicable)
- Written receipt
- Storage at the trial centers
- Documentation of the dispensing to the patients and their usage
- Return of unused medication and empty containers
- Procedure and documentation of the return to the Sponsor or the destruction of remainders

The Investigators will be responsible for ensuring the correct storage and sufficient stocks of the IMP and comparative drug at the trial centres. The Investigator bears the responsibility for the proper storage in a secure location at the site which means in a lockable cabinet with restricted access to the Investigator(s) and authorized site staff. Personnel having access to the IMP will be listed on the Authorization and Delegation log in the Investigator Site File (ISF). The Investigators will ensure that the IMP is only used according to this protocol. The Investigator will be responsible for the Drug Accountability log. Drug accountability will be noted by a monitor during site visits and at the completion of the trial. The Drug manufacturer will provide the clinical trial centre with appropriate forms to document shipments, receipt and return (or destruction) of the product.

Unused kits for preparation of [^{68}Ga]-NeoBOMB1 will be returned to the manufacturer or destroyed as per the local procedures.
Based on the stability tests performed, the NeoBOMB1 kit can be stored upon receipt at 5°C ± 3°C until the expiry date stated on the labels.

5.7 Subject compliance

Due to the nature of the drug, patient's compliance about dosing is of no concern.

6 Safety Definitions and Reporting Requirements

Safety assessments will consist of monitoring and recording AEs, including SAEs.

6.1 Adverse Events (AEs)

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

Adverse events include:

- Worsening or increase in frequency or intensity of a pre-existing disease or medical condition
- Abnormal laboratory tests

Adverse events do not include:

- Pre-planned interventions/hospitalizations
- Medical or surgical procedures, e.g. surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Diagnosis of progressive disease i.e. increase in tumour load or newly identified metastasis/complication during routine diagnostic CT.
- Overdose of either study drug or concomitant medication without any signs or symptoms that should be considered only as a specific situation.

All AEs will be reported and recorded from the signature of the ICF.

6.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following:

- Resulted in deaths

- Was life-threatening – defined as an event in which the subject was, in the judgment of the investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe
- **Required or prolonged hospitalization:** i.e. the AE requires at least a 24-hour in-patient hospitalization or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before trial entry, for social reasons or for normal disease management (including treatment adjustment) are not to be considered as SAE according to this criterion.
- **Resulted in persistent or significant disability or incapacity** (i.e. a substantial disruption of a person's ability to conduct normal life functions)
- **Was a congenital anomaly or birth defect:** i.e. an adverse outcome in a child or foetus of a subject's partner exposed to the study drug, before conception or during pregnancy.
- is medically significant, i.e. an event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition should also usually be considered as serious.

Inpatient hospitalization is defined as an overnight stay in a hospital unit and/or emergency room that includes at least one night (midnight to 06:00 AM).
The following is not considered as a SAE and should be reported as an AE only:

- Treatment of an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization

The following reasons for hospitalization are not considered as AEs or SAEs:

- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g. hospitalization for coronary angiography in a subject with stable angina pectoris
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g. hospitalization for chemotherapy for cancer, elective hip replacement for arthritis
- Hospitalization for cosmetic elective surgery, social and/or convenience reasons

6.3 Adverse Drug Reaction (ADR) & Unexpected Adverse Drug Reaction

An ADR is any noxious and unintended response to an IMP related to any dose with at least a reasonably possible causal relationship with the IMP. Briefly, an ADR is an AE which is possibly related to IMP by either the investigator or the study sponsor.
.

6.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Unexpected ADR means the nature or severity of which is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the Investigator's Brochure

A SUSAR is an adverse event, the nature or severity of which is not consistent with the applicable information available in the reference documents available for the IMP and is regarded as serious, and has at least possible relationship with the IMP.

6.5 Pregnancy

To avoid the application of the study medication during pregnancy, pregnancy tests will be performed at Screening and prior to injection. Any pregnancy that occurs during study participation must be reported to the investigator/sponsor immediately (no later than SAEs reporting timelines). If a pregnancy should be confirmed after informed consent has been obtained but prior to the initiation of the study drug, the patient must be excluded from the trial. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications (including spontaneous abortions) and elective terminations must be reported as an AE or SAE.
Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the IMP, must be promptly reported to the sponsor.
As the consent for the study does not cover the consent for the follow-up of the pregnancy, a separate consent must be obtained.

6.6 Severity of adverse events / Grading

Intensity of all adverse events will be graded according to the Toxicity Grading Scale vaccine clinical trials (Appendix 2) and reported in detail in the Case Report Form (CRF).
Adverse events not listed in the Toxicity Grading Scale vaccine clinical trials should be graded as follows:

CTC grade	Equivalent to	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity and does not require mandatory corrective/symptomatic treatment
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention (other than minimal) is indicated although this could improve the overall wellbeing or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated to improve the overall wellbeing or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening / disabling	An immediate threat to life or leading to a permanent mental or physical condition that prevents work or performing normal daily activities; treatment or medical intervention is required to maintain survival.

Grade 5	Death	AE resulting in death

6.7 Relationship to study drug

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information and considering all relevant factors such as (but not limited to) the underlying indication, coexisting diseases, concomitant medication, etc. at the time of the completion of the case report form.
Is there a reasonable possibility that the study drug caused the event?
Answer **YES** (definitely, probably or possibly related) if one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.

The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).
Otherwise answer **NO** (unlikely, probably not related or definitely not related).

6.8 Reporting procedures for AEs

A special section is designated to adverse events in the CRF where the following details must be entered:

- Type of adverse event (diagnosis or syndrome; if not known signs or symptoms) and brief description (including context of occurrence)
- Start (date)
- End (date)
- Severity (mild, moderate, severe, life-threatening/disabling, death)
- Serious (no / yes)
- Outcome (resolved, ongoing, ongoing – improved, ongoing – worsening) and recovery date
- Action taken (none, study medication dose reduced, study medication interrupted, study medication discontinued, medication therapy, surgical procedure, hospitalization, other)
- Relation to study drug (possibly, probably or definitely related or unlikely, probably not related or definitely not related)
- Treatment date with the IMP (in order to estimate the time to onset)

- Patients relevant medical history and/or concomitant treatments that may provide alternative explanation regarding the AEs occurrence.

6.9 Reporting procedures for SAEs

When an SAE is made known to the Principal Investigator (PI) or other site personnel, it must be reported to AAA Pharmacovigilance within the best timelines and no more than 24 hours (one calendar day) of knowledge of the event.

The responsibilities of the PI include but are not limited to:

- Identifying the SAE (detailed description) and providing the criteria of seriousness,
- Assessing causality/relationship of the SAE to investigational product,
- Determining the severity/intensity according to the protocol and event outcome,
- Determining the event onset and resolution dates,
- Maintaining adequate documentation of the SAE and all communications relating to the event including communications with the subject, treating physician, AAA Pharmacovigilance, CRO

The SAE reporting process is described below:

- Complete an SAE report form. The SAE report form must be documented in English and any supporting documentation (e.g. event narrative or discharge summary) must be briefly summarized in English in the SAE report. Unless otherwise requested by AAA Pharmacovigilance, only death certificates and autopsy reports may be submitted as separate documents. Discharge summary translated in English may also been provided upon Sponsor (AAA) request
- Provide as much information as is known at the time the initial report is submitted to AAA Pharmacovigilance. The elements required to make an initial assessment of the event to meet reporting obligations to health authorities are:
    - ✓ Site number (4-digit) and subject number (3-digit) and subject initials (if local privacy laws allow),
    - ✓ Serious event description plus all seriousness criterion that apply (e.g., hospitalization, etc),
    - ✓ Relationship to investigational product (causality assessment),
    - ✓ Severity/intensity grade as available,
    - ✓ Start date of event,
    - ✓ Investigational product administration details (i.e., dose, regimen, and therapy dates),
    - ✓ Outcome at time of initial reporting
    - ✓ Reporter name, Investigator name, phone number, and email address.
- Fax or email the completed SAE report form to AAA Pharmacovigilance using the fax number or email address located on the SAE report form or in the SAE Completion Guidelines (Fax: [redacted], E-mail: [redacted]) .

Site personnel will retain a record of faxed/emailed SAE report forms in the site file; i.e., print the confirmation of successful transmission from the fax machine or a copy of sent email. If a fax print-out is unavailable, a written notation of fax date and time on the coversheet is acceptable.

- Fax/email relevant follow-up information to AAA Pharmacovigilance, within 24 hours of receiving the information, via a Follow-up SAE report form, including, but not limited to:
    - ✓ Start and stop dates of event,
    - ✓ Action(s) taken regarding investigational product(s),
    - ✓ Event outcome,
    - ✓ Discharge summary (e.g., diagnostic test reports, x-ray reports, discharge summaries or autopsy report, if applicable to the SAE(s) being reported),

NOTE: The Investigator and other site personnel must ensure subject confidentiality is maintained when reporting SAEs to AAA Pharmacovigilance. The site should review the supporting documentation to ensure complete redaction of any subject identifying information prior to forwarding to AAA Pharmacovigilance.

6.10 Reporting to the competent authorities and IRB/IEC

The Sponsor or representative will assume responsibility for appropriate reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) and any new safety data which jeopardize the safety of any volunteer to the Competent Authorities (CA) and Independent Ethics Committee(s)/Institutional Review Board(s) (IEC/IRB) according to local laws and regulations.

The Sponsor will inform CA, IRB/IEC, and Investigators of “findings that could adversely affect the safety of subject and impact the conduct of the study or alter the IRB/IEC’s approval/favourable opinion to continue the study”. The Sponsor will inform about adverse events from other trial sites, other clinical studies with the same product, or from post-marketing setting as applicable, depending on the stage of development of the product, which are both serious and unexpected and whose causal relationship with the administered product was considered as definitely, possibly or probably related by the Investigator.

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

6.11 Adverse Event Reporting Period

All AEs will be reported and recorded from the signature of the ICF.
Investigators will seek information on AEs at each patient contact throughout the trial. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient’s medical record and on the Adverse Event part of the application day Case Report Form (CRF).

After informed consent has been obtained all AEs and SAEs regardless of relationship to the study drug will be reported until FU3 or until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.
After FU3, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with the study drug.
Any Serious Adverse Event (SAE) that is ongoing at the time of FU3 should be followed-up until resolved.

6.12 Annual Safety Report

Once per year, the sponsor or PI will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent authorities of all other member states of the Europe where the trial is being conducted. This report will also be supplied to the responsible ethics committee.
The annual safety report will be compiled according to the corresponding ICH guideline E2F ”Development Safety Update Report – DSUR“
The data lock point for the DSUR will be the day prior to the anniversary of the date of the first authorization of this clinical trial.
The sponsor will supply the report within 60 from the data-lock point.

7 Statistical considerations

7.1 Sample Size & Randomization

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. In addition, no randomization is required due to the study design. It is anticipated that 50 patients with malignancies known or suspected to overexpress GRPR will be recruited in the trial and will undergo application of [^{68}Ga]-NeoBOMB1 and PET-CT imaging. It is expected that a large proportion of these patients will be GRPR positive according to histopathology / cytology data but that patients will also be recruited whose tumours do not show GRPR 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 example, 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 tumour types included in the trial. Although it won’t be possible to make strong conclusions within the tumour types, this should ensure that a reasonable number of GRPR

positive patients are available within each tumour type and this will allow initial estimates of diagnostic properties to be made and will ensure each tumour 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, biodistribution and dose-limiting critical organs. Data from all 50 patients in the trial will be used to assess all other study objectives.

7.2 Statistical Design, Method and analytical Procedures and Definition of Populations

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. The Per Protocol (PP) set consists of all patients of the FAS set who complete the study according to the protocol with no major protocol violations. All analyses will primarily be performed on the FAS, select analyses may be repeated on the PP set if there are sufficient violations to warrant it and deviation of results by using the PP set will be discussed. All data will be listed and summary tables of the data will be given.
Statistical methods will be detailed in the Statistical Analysis Plan (SAP).

The primary focus of the statistical analysis will be on descriptive statistics and graphical presentations of data. Continuous variables will be presented as number of non-missing values, mean, standard deviation, median, minimum, maximum and quartiles. For categorical variables, descriptive statistics will include counts and percentages per category. Confidence intervals will be computed when appropriate. Continuous variables will be compared where relevant using the most appropriate test such as paired analysis Mann-Whitney-Wilcoxon U test or paired analysis Student's *t* test. Proportions will be compared using the appropriate test among Chi squared test, Fisher exact test or McNemar test. Pearson's or Spearman linear regression analysis will be used to explore potential relationships between two continuous variables as appropriate. Any hypothesis testing that is performed will be interpreted as exploratory and no emphasis will be placed on nominal significance levels.

No adjustment for multiplicity will be applied and missing data will not be replaced.

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

7.3 Efficacy Analysis

<u>Primary endpoint:</u>

- The preliminary targeting properties of [^{68}Ga]-NeoBOMB1 will be assessed by summaries of the number and location of lesions identified by PET, SUV values per

lesion, tumour background ratio of [^{68}Ga]-NeoBOMB1 and the percentage of injected dose reaching the target presented split by GRPR positive and negative patients. Tumour uptake will be evaluated by Standard Uptake Value. SUV_{mean} and SUV_{max} will be determined and summarized descriptively.

- The tumour-background ratio of [^{68}Ga]-NeoBOMB1 and the percentage of injected dose reaching the target will be calculated using the acquired images resulting in time-activity curves (TACs) with quantitative fractions of administered activity and summarized descriptively.

Secondary endpoints:

- The [^{68}Ga]-NeoBOMB1 bio-distribution, pharmacokinetics, dosimetry and absorbed dose in critical organs will be determined by calculation of TACs measured by a NaI gammacounter from blood and urine and stability will be analysed using HPLC measurements. Regions of interest (ROI) for critical organs and tumour lesions will be drawn using the acquired images resulting in time-activity curves with quantitative fractions of administered activity. Dosimetry calculations will be issued from the analyses of organs receiving the highest dose, identified visually. ROI will be placed over these organs to determine relative radiotracer uptake calculated as a percentage of the injected dose per gram of tissue (%ID/g). Tissue activity curves will be generated from the amount of radioactivity in one given tissue at a given moment considering renal excretion activity. Tissue ACs will be fitted to mono- and bi-exponential curves to yield cumulative activities. Urine samples 0-2h and 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. Effective radiation dose will be summarized descriptively.
- Tumour uptake will be evaluated by Standard Uptake Value. SUV_{mean} and SUV_{max} will be determined and summarized descriptively.
- Number of observed tumour lesions and localization in PET/CT will be summarized descriptively overall and split by GRPR positive and negative patients, as well as by tumour type, and will be compared to the number of observed lesions and localization in a comparable conventional imaging.
- 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. This will also be repeated splitting by GRPR positive and negative patients and also by primary tumour type of patients in the trial.
    - On a lesion level overall, positive and negative agreement of [^{68}Ga]-NeoBOMB1 will be calculated 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 level of discordance between the two imaging techniques where appropriate, acknowledging issues with lack of independence of observations on a lesion level.

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

- [^{68}Ga]-NeoBOMB1 PET preliminary diagnostic performance relative to cytology and/or histopathology findings from archival and/or recent biopsy specimens will be assessed primarily on a patient level, but also on a lesion level for lesions with associated biopsy data available.
  - On a patient level, patients with at least one positive PET imaging lesion identified versus those without any PET imaging lesions identified will be cross-tabulated with whether or not they have at least one biopsy with GRPR expression identified. Sensitivity and specificity values will be calculated as appropriate.
  - On a lesion level, positive and negative PET imaging lesions will be cross-tabulated with their GRPR positive or negative status according to biopsy data and sensitivity and specificity values will be calculated as appropriate. Appropriate tests of association may also be performed if relevant.

  Potential relationships between [^{68}Ga]-NeoBOMB1 PET targeting properties and cytology and/or histopathology findings may also be explored using alternative endpoints where appropriate. For example, continuous measures of GRPR expression may be correlated against each patient proportion of conventional imaging lesions also detected by [^{68}Ga]-NeoBOMB1 PET imaging using scatterplots and simple linear regression models.

7.4 Safety Analysis

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

All original AE/SAE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be listed on an individual basis and will be summarized by System organ classes and preferred terms will be used in the analyses. Patients with more than one adverse event within a particular SOC and PT will be counted only once for that SOC and PT. The type and incidence of AEs/SAEs, as well as severity and relatedness to the investigational product will be tabulated.

7.5 The treatment of missing, unused or spurious Data, including Drop-outs and Withdrawals

No specific procedures for handling of missing, unused and spurious data will be pre-determined.

8 Documentation

The accomplishments of the study in agreement with the GCP-guidelines and the investigational plan as well as the accuracy of all data documented in the e-CRF are the responsibility of the Investigator. All data of this study must be recorded on the e-CRF by appropriate authorized persons. This also includes data of patients who dropped-out of the study.
The Investigator records the participation on a special identification list of patients. This list gives the possibility for a later identification of the patients and contains the patient number, full name, date of birth and the date of the enrollment into the study. The identification list of patients remains in the study centre after the closure of the study. Additionally, the participation of the patient in this clinical study must be recorded in the patient`s medical record (investigational medicinal product, number of patient or randomization, start and end of the study).
It must be assured that all persons authorized for e-CRF entries can be identified. A list with signatures and identification codes of the persons must be archived in the ISF and Trial Master File (TMF). Furthermore, logs according to ICH E6 (e.g. Signature/Delegation/Screening/Drug Accountability log) will be implemented and maintained by the Investigator.

8.1 Recording of Data

Data collection for each patient is done using a e-CRF. This e-CRF is filled up by the Investigator, according to the completion guidelines.
For each patient enrolled, a eCRF must be completed, signed and dated by the Investigator or by his/her authorized designee(s) according to the Signature/Delegation Log. This also applies to subjects failing to complete the study (Drop-Outs).
The Investigator assures that all data are recorded immediately, are complete, correct and in agreement with the patient`s medical records.

A copy remains at the Investigator and will be kept for 15 years.

8.2 Trial Master File

The paper-based/electronic TMF, established at the beginning of the trial and secured in a safe place, contains all essential documents that demonstrate that the trial is conducted in accordance with regulatory requirements and ICH GCP. All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the TMF and will be clearly labelled as outdated. The TMF is archived at the end of the study for 15 years.

8.3 Investigator Site File

The paper-based ISF, established at the beginning of the trial will be secured in a safe place (the file is provided to the sites at the site initiation visit). It contains all essential documents maintained by the PI(s). All documents will be maintained and updated as appropriate throughout the trial. Previous versions of the documents must be retained in the ISF and will be clearly labelled as superseded. Within each monitoring visit, the ISF will be checked for actuality and completeness in accordance to the formalities by the Clinical Research Associate (CRA). After completion or discontinuation of the study the ISF must be kept for 15 years.

8.4 Storage of Data

8.4.1 Storage Duties of the Sponsor

The Sponsor must keep all study-relevant documents of the clinical study after completion or discontinuation of the study for a minimum of 15 years in the TMF.

8.4.2 Storage Duties of the Investigator

The Investigators must keep all records and documents, which are related with the study or the allocation of investigational medicinal products (e.g. data entry form, consent form, list of the allocations of investigational medicinal products and further relevant documents), for a minimum of 15 years in the ISF.
Medical records and other original data must be kept for 30 years.

9 Quality Control and Quality Assurance

Training, monitoring and audits are performed for quality assurance reasons within this clinical study. Monitoring and auditing procedures developed or endorsed by the Sponsor will be

adhered to, to comply with ICH-GCP guidelines and local legal requirements to ensure acceptability of the study data.

9.1 Training

The Sponsor is responsible for selecting the Investigator(s)/Institution(s). Each Investigator should be qualified by training and experience and should have adequate resources. Everyone involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s) (see ICH GCP E6).
Investigators will have to have experience in the field of clinical imaging studies.

9.2 Clinical Monitoring

The trial sites will be monitored by CRAs to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected. In addition, it is to ensure accurate, valid and complete data are collected, and that the trial is conducted in accordance to the trial protocol, the principles of GCP and local legislation.
All Investigators agree that the CRA regularly visits the trial site and assure that the CRA will receive appropriate support in their activities at the trial site, as agreed in separate contracts with each trial site. The ICF includes a statement that the CRA has the right – while observing the provisions of data protection legislation – to compare CRFs with the trial subject's medical records (doctor's notes, ECGs, laboratory printouts etc.). The Investigator will secure access for the CRA to all necessary documentation for trial-related monitoring.
A study specific monitoring plan will be established and the study will be monitored with the agreed plan.

9.3 Auditing

Regulatory authorities, the ethics committees, and Sponsor's delegates may perform on-site inspections or audits, for which the Investigator must grant direct access to all data and must provide support at all times.
The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The Sponsor may assign these activities to persons otherwise not involved in the trial (Auditors). These persons are allowed access to all trial documentation (especially the trial protocol, CRFs, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).
After each external audit an audit-certificate by the Auditor must be delivered to the Investigator. This certificate must be kept in the ISF to evidence the audit to the regulatory authorities in the case of an inspection by them. The audit-report is delivered to the Sponsor of the study. An audit-certificate will be attached to the final report at the end of the study. Additionally, audits and inspections by regulatory authorities may be performed.

All persons conducting audits undertake to keep all trial subject data and other trial data confidential.

10 Reporting

10.1 Final Study Report

All information regarding this clinical study must be kept in confidence. The statistical analysis and the integrated final study report will be prepared according to ICH E6 and finalized within 12 months after the Last Patient Last Visit (LPLV) took place. The final study report will be reviewed and signed by the Sponsor, the Coordinating Investigator and all further responsible persons. All information in that report is strictly confidential.

10.2 Publication/Data sharing Policy

The Investigator/Institution will not publish the results of the trial without the prior written consent of the Sponsor, which permission shall not be unreasonably withheld. If the Sponsor grants such permission, the Investigator/Institution agrees to submit a copy of any manuscript and/or abstract to the Sponsor for review and comment at least 90 days prior to its submission for publication. The Sponsor shall have the applicable 90-day period to respond to the Investigator/Institution with any revisions. Investigator/Institution agrees to delete any confidential information identified by the Sponsor at the Sponsor's sole discretion, prior to submitting such manuscript and/or abstract for publication. If reasonably requested by the Investigator/Institution, the Sponsor will take reasonable steps to expedite the review process to less than the 90-day period to meet Investigator's/Institution's publication deadlines, but the Sponsor is under no obligation to expedite the review process. Upon notification by the Sponsor that such review has been completed, Investigator/Institution may submit the manuscript and/or abstract for publication after deleting any confidential information identified by the Sponsor.

11 Ethical and Regulatory Aspects

11.1 Good Clinical Practice and Declaration of Helsinki

The procedures set out in this study protocol are designed to ensure that the Sponsor and the Investigator abide the principles of ICH E6 recommended for adaptation in June 2015 by the ICH Steering Committee and according to the Declaration of Helsinki of 2013 concerning the conduct, evaluation and documentation of the study. The study will also be performed adhering the local legal conditions and requirements. Each Investigator must confirm this by signing the study protocol.

11.2 Approval of the Study

Prior to study start, the study protocol and/or other appropriate documents will be submitted to the relevant ECs and CAs for approval. Approval from all concerned ECs and CAs must be obtained before starting the study.

11.3 Insurance

During their participation in the clinical trial the patients will be insured as defined by legal requirements. The sponsor is providing insurance to indemnify (legal and financial coverage) the investigator/trial centre against claims arising from the study, except for claims that arise from malpractice and/or negligence. The compensation of the subject in the event of study-related injuries will comply with the applicable regulations.

11.4 Confidentiality

All local legal requirements regarding data protection will be adhered to. All study findings and documents will be regarded as confidential. The Investigator and members of the research team must not disclose any information without prior written approval from the Sponsor.
The pseudonymity of patients participating must be maintained. Throughout documentation and evaluation, the patients will be identified on CRFs and other documents by a patient IDs. Documents that identify the patient personally (e.g., the signed informed consent, patient identification list) must be maintained in confidence by the Investigator. *The patients will be informed in the ICF that all study findings will be stored on paper and handled in strictest confidence.*

12 Amendments

Amendments must be submitted to the appropriate CAs and ECs. Substantial amendments may be implemented only after CA/EC approval has been obtained. Urgent amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving CA/EC approval. However, approval must be obtained as soon as possible after implementation. Therefore, the sponsor must inform the CA and the EC concerned of the new events, the measures taken and their plan for further action as soon as possible.

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14 Supplements/Appendices

14.1 Appendix 1: Toxicity Grading Scale vaccine in clinical trials

A. **Tables for Clinical Abnormalities**

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

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension

Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

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

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

event (as defined according to applicable regulations)		with activity not requiring medical intervention	requires medical intervention	

B.Tables for Laboratory Abnormalities

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

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23-26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN

Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.
***ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic

Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	ï€ 1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

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

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

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