PROTOCOL TITLE: A multicentre, randomised, dose-confirmation, factorial phase II study to evaluate the optimal dose of ^{68}Ga-OPS202 as a PET imaging agent in subjects with gastroenteropancreatic neuroendocrine tumour (GEP-NET)

STUDY PROTOCOL
STUDY Number: D-FR-01070-002

^{68}Ga-OPS202
EudraCT Number: 2016-004928-39/NCT Number: XXXX

Version 5.0, Amendment 3.0: 20 May 2019

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01070-002 entitled "A multicentre, randomised, dose-confirmation, factorial phase II study to evaluate the optimal dose of ^{68}Ga-OPS202 as a PET imaging agent in subjects with gastroenteropancreatic neuroendocrine tumour (GEP-NET)". I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
[ ]
[ ]
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Sponsor's Representative Signature:

NAME: PPD

TITLE: PPD Ipsen Biopharm Ltd

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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01070-002 entitled "A multicentre, randomised, dose-confirmation, factorial phase II study to evaluate the optimal dose of ^{68}Ga-OPS202 as a PET imaging agent in subjects with gastroenteropancreatic neuroendocrine tumour (GEP-NET)". I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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SUMMARY OF CHANGES

The current version of the protocol was released on 20 May 2019 and includes Amendment 3.0. For all protocol amendments, amendment forms were prepared and are provided in the Appendices listed in Table 1. All modifications (except minor changes) are presented in the appendices.

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
Original (Version 2.0)	30 March 2017	Appendix 2
1.0 (Version 3.0)	16 June 2017	Appendix 3
2.0 (Version 4.0)	03 May 2018	Appendix 4
3.0 (Version 5.0)	20 May 2019	Appendix 5

SYNOPSIS

Name of sponsor/company: IPSEN	
Name of finished product: ^{68}Ga-OPS202 - ^{68}Ga-satoreotide trizoxetan **Name of active ingredient(s)**: ^{68}Ga-OPS202 - INN for OPS202 is satoreotide trizoxetan	
Title of study: A multicentre, randomised, dose-confirmation, factorial phase II study to evaluate the optimal dose of ^{68}Ga-OPS202 as a PET imaging agent in subjects with gastroenteropancreatic neuroendocrine tumour (GEP-NET) **Study number**: D-FR-01070-002	
Number of planned centres: Six specialised centres in the United States and Europe	
Planned study period: FPI: June 2017 - LPO: September 2019	**Phase of development**: Phase II

Objectives:

Primary Study Objective:

- To define the optimal dose range for peptide mass and radioactivity of ^{68}Ga-OPS202 based on detected lesions in adult subjects with somatostatin receptor 2 (sstr2)-positive gastroenteropancreatic neuroendocrine tumour (GEP-NET).

Secondary Study Objectives:

- To further refine the optimal dose range for peptide mass and radioactivity of ^{68}Ga-OPS202 based on quantitative maximum standardized uptake value (SUV_{max}) and other quality parameters.
- To describe the safety and tolerability of diagnostic ^{68}Ga-OPS202 in subjects with sstr2-positive GEP-NET.
- To characterize the pharmacokinetics (PK) of OPS202 in subjects with GEP-NET.

Exploratory Objective:

- To provide preliminary estimates of the sensitivity of ^{68}Ga-OPS202 positron emission tomography/computed tomography (PET/CT) scan imaging, as well as SUV ratio (SUV_{max} lesion/ SUV_{mean} reference tissue) and signal-to-noise ratios (SNR).

Methodology:

Study design

This is a multicentre, multinational, randomised, open-label, reader-blinded, dose-confirmation, 2 × 3 factorial phase II study, with an approximate 7-week duration.

Two target peptide mass dose ranges (5-20 µg and 30-45 µg), and three radioactivity dose ranges (40-80 megabecquerels [MBq], 100-140 MBq and 160-200 MBq activity of ^{68}Ga) of ^{68}Ga-OPS202 will be investigated to provide information on different possible peptide/radioactivity dose range combinations that are summarized in table below.

Combinations of Studied Peptide Mass Dose Ranges and Radioactivity Dose Ranges

Peptide mass dose range	Radioactivity dose range		
	40-80 MBq	100-140 MBq	160-200 MBq
5 – 20 µg	8 scans	8 scans	8 scans
30 – 45 µg	8 scans	8 scans	8 scans

Each of the 24 evaluable subjects will receive two different peptide/radioactivity ranges combinations. Hence, 48 PET/CT scans will be analysed (8 in each combination peptide/radioactivity dose range)

The lowest peptide mass dose range with the highest radioactivity dose range can only be obtained with a new ^{68}Ge/^{68}Ga-generator. It is anticipated that the 40 to 80 MBq radioactivity dose range will provide a poor diagnostic signal, particularly for subjects with a high body mass index (BMI). However, with the "as low as reasonably achievable" (ALARA) principle, this will be studied as well as the higher peptide mass dose.

^{68}Ga-OPS202 consists of 50 µg of peptide in a total volume of 6 mL (8.33 µg/mL). Sampling of 0.5 mL for quality control yields 5.5 mL solution from which the volume to be injected into the subject is withdrawn. This volume is calculated to obtain the target peptide mass dose and the desired radioactivity dose, taking into account the elapsed time between the syringe preparation and the intravenous (i.v.) administration of ^{68}Ga-OPS202 (decay of ^{68}Ga).

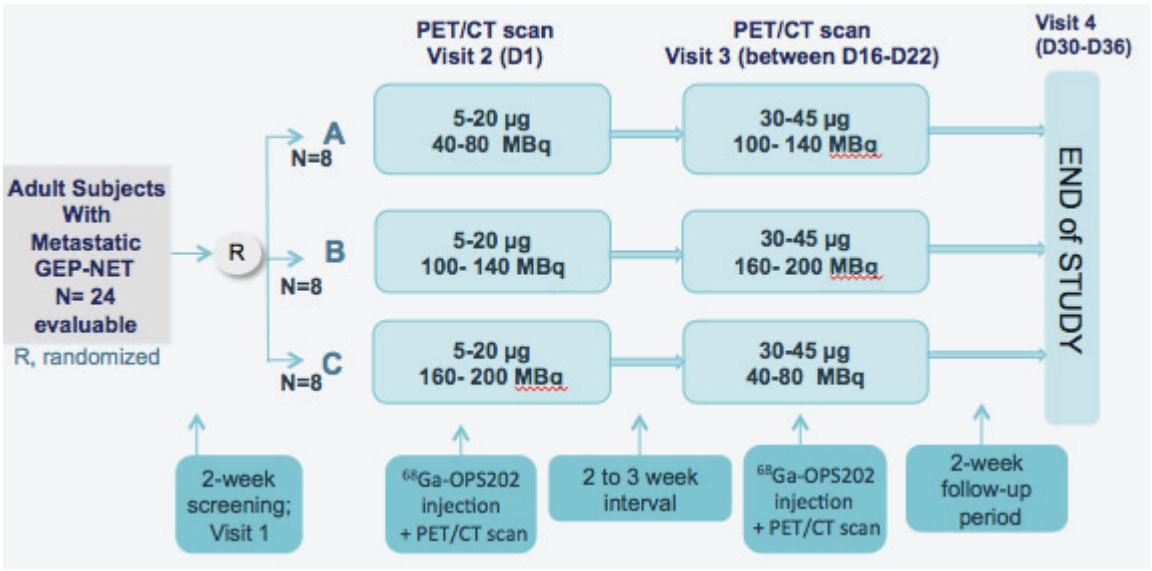
Subjects will be assigned to one of three study arms (see figure). At the end of the study, each subject will provide two sets of images corresponding to two combinations of peptide / radioactivity dose ranges. The sets of images for the primary endpoint, and most of the secondary endpoints will be sent to an imaging core lab (ICL) for central blinded reading by two independent experienced radiologists and a third for adjudication of discordances. The readers will be specifically trained for this protocol.

All decisions regarding subjects' medical management will be made locally by the treating physicians (images read locally for this purpose). The ICL/central readers will only evaluate the study endpoints and will not make any decisions regarding subject management.

Duration of participation for a subject

Subject participation in the study is estimated to last approximately 7 weeks and will include:

- Visit 1: A screening period up to 2 weeks
- Visit 2: A single i.v. injection of the first peptide/radioactivity dose of ^{68}Ga-OPS202 on Day 1 followed by PET/CT scan imaging 1 hour post dosing (up to 80 min)
- Visit 3: A single i.v. injection of the second peptide/radioactivity dose of ^{68}Ga-OPS202 followed by PET/CT scan imaging 1 hour post dosing (up to 80 min), after a 15- to 21-day time interval from the first administration (Visit 2)
- Visit 4: A 2-week follow-up period for evaluation of safety.



Study Design and Subject Allocation

Assessments

At the Screening Visit (Visit 1) performed within 2 weeks prior to the first ^{68}Ga-OPS202 administration, the investigator will collect all the information required to check the eligibility of the subject to participate in the study including medical and surgical history, physical examination, laboratory tests (including haematology, blood chemistry and urinalysis) and tumour histopathology. Results from a somatostatin receptor positive scan within 6 months prior to the first ^{68}Ga-OPS202 administration will be collected and sent to the ICL for assessment of quality and admissibility.

Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before randomisation. If the eligibility is confirmed, the subject will be randomly allocated to one of the three study arms to receive the first dose of ^{68}Ga-OPS202 with PET/CT imaging, then discharged the day after. Intravenous iodinated CT contrast is required and will be injected according to the site standard procedure. This procedure will be repeated after 15 to 21 days at Visit 3 (Day 16 to 22) with the appropriate peptide/radioactivity dose range combinations of ^{68}Ga-OPS202 as indicated by the subject's randomisation. The PET/CT scanner must be the same for the two scans per subject and for all subjects at the same study site. Subjects may be hospitalised overnight at the discretion of the investigator.

For OPS202 PK, blood samples of 2 mL will be collected at the following timepoints: Baseline pre-dose (T0), 5 min, 15 to 45 min, 1h, 2h, 3h and 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits (Visit 2 and Visit 3). Urine will also be collected during the first 6 hours in two separate samples: 0h to 3h and 3h to 6h after the ^{68}Ga-OPS202 i.v. administration.

An End of Study Visit (Visit 4) will take place 2 weeks after the second PET/CT scan, during which the investigator will collect the safety information required by the study protocol (See Criteria of Safety Evaluation below). At the end of Visit 4, the subject's participation in the study will end. For any adverse event (AE) emerging or worsening during the study that persists beyond Visit 4, the investigator will monitor the subject until the AE is resolved or considered stabilized.

Comparative methods and blinding

This is an open-label study. Independent readers will evaluate ^{68}Ga-OPS202 PET/CT images and will be blinded to the investigator site and clinical status of the subject, including pathology, laboratory, and history/physical exam findings. Furthermore, the independent readers will be blinded to peptide mass dose, radioactivity dose, and the temporal sequence of dosing.

Independent readers are specialized radiologists and/or nuclear medicine physicians who are experienced in reading ^{68}Ga-radiolabeled agent PET/CT scans. To minimize inter- and intra-reader variability in results, the readers will be specifically trained for this protocol.

Number of subjects planned:

A total of 24 evaluable subjects with GEP-NET and two ^{68}Ga-OPS202 PET/CT scans completed are required (8 subjects in each of the three study arms). A total of at least 25 subjects will be enrolled in the study to ensure the 48 PET/CT scans for the analysis (see below Sample size and power considerations)

Diagnosis and criteria for inclusion:

Following a screening period of up to 2 weeks, eligible subjects will be enrolled in the study if they meet all the following inclusion criteria, and none of the following exclusion criteria:

Inclusion criteria:

1) Men or women aged 18 years or older
2) Subjects with pathologically confirmed, well-differentiated functioning or nonfunctioning metastatic GEP-NET (Grade I and II as per World Health Organization (WHO) classification 2010)
3) Subjects with a confirmed presence of somatostatin receptors (type 2) on technically evaluable tumour lesions documented by a positive somatostatin receptor scan within 6 months prior to screening (Visit 1) and showing a minimum of two lesions in at least one of the key organs namely liver, lymph nodes, bone or lungs; these images shall be available to be sent to the ICL electronically to ascertain quality and admissibility
4) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
5) Subjects with body weight between 50 kg (110 lb) and 110 kg (243 lb), inclusive
6) Adequate bone marrow, liver and renal function, with:

- Calculated glomerular filtration rate (GFR): ≥ 45 mL/min

- Albumin: > 30 g/L
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP): ≤ 5 times ULN (upper limit of normal)
- Bilirubin: ≤ 3 times ULN (3 × 1.1 mg/dL)
- Leukocytes: ≥ $3*10^9$/L and neutrophils ≥ $1*10^9$/L
- Erythrocytes: ≥ $3.5*10^{12}$/L
- Platelets: ≥ $90*10^9$/L

7) Signed written informed consent prior to any study-related procedures

Exclusion criteria:

1) Subjects with fewer than five lesions in total and more than 25 lesions/organ detected by the somatostatin receptor positive scan in key organs: liver, lymph nodes, bone or lung
2) Subjects who have received treatment of any somatostatin analogue, including Somatuline® Autogel® /Depot®, Sandostatin® LAR within 28 days, and Sandostatin® within 24 hours prior to first ^{68}Ga-OPS202 administration
3) Presence of active infection at screening or history of serious infection within the previous 6 weeks prior to the first ^{68}Ga-OPS202 administration
4) Prior or planned administration of a radiopharmaceutical within 8 half-lives of the radionuclide
5) Clinically relevant trauma within 2 weeks prior to first ^{68}Ga-OPS202 administration
6) Known hypersensitivity to radiolabeled 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (NODAGA), to Gallium-68, to somatostatin analog peptide JR11 (JR11) or to any of the excipients of ^{68}Ga-OPS202
7) History of, or current active allergic or autoimmune disease, including asthma or any condition requiring long-term use of systemic corticosteroids
8) Known human immunodeficiency virus (HIV) or positive serology for HIV, hepatitis B or C
9) Any condition that precludes the proper performance of PET and/or CT scan:
   - Subjects who are not able to tolerate the CT contrast agent,
   - Subjects with metal implants or arthroplasty, or any other objects that might interfere with the PET and/or CT analysis
   - Subjects unable to raise arms for prolonged imaging purposes
   - Subjects unable to lie still for the entire imaging time
   - Subjects weighing greater than 110 kg (243 lb)
10) Administration of another investigational medicinal product within 30 days prior to first ^{68}Ga-OPS202 administration
11) Female subjects who are pregnant, breast feeding or of childbearing potential not willing to practice effective contraceptive techniques during the study treatment period and for 30 days after the last dose of ^{68}Ga-OPS202 administration; pregnancy test must be performed at the start of the study and prior to each ^{68}Ga-OPS202 administration
12) Subjects who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, including any mental

condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude

13) Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus and/or subjects treated with curative intent and free from disease for more than 5 years) other than NET.

Test product, dose, mode of administration:

^{68}Ga-OPS202 is a diagnostic medicinal product with 3 main components, namely:

- ^{68}Ga, a positron emitter radionuclide with a half-life of 68 min
- NODAGA, a chemical chelator group, and
- JR11, an antagonist somatostatin analogue that binds to sst2 receptors

OPS202 (cold kit) is available for clinical trials in a 50 µg peptide mass dose vial and is radiolabeled using a ^{68}Ge/^{68}Ga-generator. The radiolabelled OPS202 (^{68}Ga-OPS202) consists of 50 µg of peptide in a total volume of 6 mL (8.33 µg/mL). Sampling of 0.5 mL for quality control yields 5.5 mL solution from which the volume to be injected into the subject is withdrawn. This volume is calculated to obtain the target peptide mass dose and the desired radioactivity dose.

The calculation of the volume takes into account the different components that determine the final radioactivity dose. The subject will be exposed to, in particular:

- The amount of ^{68}Ga eluted from the generator, which depends on the latter's half-life
- The time elapsed between OPS202 (cold kit) radiolabelling and the injection of ^{68}Ga-OPS202 to the subject (decay of ^{68}Ga), the variation of which is a tool to adjust the final peptide/radioactivity dose to be injected
- The required peptide mass dose and radioactivity dose of ^{68}Ga-OPS202 to be injected.

The actual peptide mass dose administered to the subject (injected dose) will be estimated using the following equation:

Injected dose (µg) = [Volume injected (mL) / Volume used for ^{68}Ga-OPS202 preparation (mL)] x Peptide dosage in the vial (µg) = [Injected Volume/6mL] x 50µg

The radioactivity in the syringe is measured immediately before the administration of ^{68}Ga-OPS202 to the subject and immediately after; the difference between these two measurements (in MBq) constitutes the radioactivity dose injected to the subject.

^{68}Ga-OPS202 will be administered twice during the study for each subject by i.v. injection over one minute prior to PET/CT scan. The PET/CT scanner settings should be the same for the two scans per subject and for all subjects at the same study site, as described in the Imaging Review Charter (IRC).

Duration of treatment: ^{68}Ga-OPS202 will be administered i.v. twice: at Baseline/Day 1 (Visit 2), and at Visit 3, which will be 15 to 21 days after the first injection.

Reference therapy, dose and mode of administration:

Comparator compound/placebo:

In this study, there is no comparison with a placebo or reference-imaging product. The statistical analyses will describe the differences between the different combinations of peptide mass dose range and radioactivity dose range.

Other treatments: Any medication and/or therapy taken or received by the subject during the study, other than the study investigational compound (^{68}Ga-OPS202), will be considered concomitant medication whether or not it is targeting the studied GEP-NET. Concomitant treatments are to be prescribed, modified, or discontinued at the investigator discretion. Subjects must be withdrawn from the study, but followed-up when possible for further data collection, if at least one of the protocol-prohibited medications/therapies (see above-mentioned eligibility criteria) is received by the subjects during the study period up to the end of the second PET/CT scan (at Visit 3).

Any addition, change, or discontinuation of concomitant medications should be documented as defined in the study protocol.

Criteria for evaluation:

Efficacy:

All the primary and secondary imaging endpoints are read by third-party independent readers. Most of the reading will be conducted in blinded manner. Primary and secondary endpoints will be measured in key organs: liver, lymph nodes, bone and lungs.

Primary Endpoint and Evaluation:

- For each combination of injected peptide/radioactivity dose ranges, differences in relative lesion counts derived from a 2 × 3 factorial analysis measuring the ratio of the number of lesions detected by ^{68}Ga-OPS202 to the number of lesions assessed by standard-of-truth (descriptive analyses).

The standard-of-truth in the present study is the CT scan images acquired at Visit 2 and Visit 3.

Secondary endpoints and evaluations:

Key secondary endpoint:

- For each combination of injected peptide/radioactivity dose ranges, differences in image quality derived from a 2 × 3 factorial analysis measuring the tumour-to-background ratio in each of the major anatomic sites (descriptive analyses for liver, lymph nodes, bone and lungs)

A qualitative analysis of the image assessed by the independent blinded readers will be performed to back up the quantitative quality measured by tumour-to-background analysis.

Other secondary endpoints:

- Differences in lesion SUV_{max} between the two peptide mass dose ranges and the three radioactivity dose ranges measured in the most avid lesions (descriptive analyses for up to a maximum of five lesions per organ in liver, lymph nodes, bone and lungs)
- Differences of absolute number of lesions between the two peptide mass dose ranges and the three radioactivity dose ranges detected in each of the following anatomic sites:

- Primary site of GEP-NET
- Lymph nodes
- Liver
- Axial/appendicular skeleton
- Lungs

The primary and secondary endpoints will also be evaluated on a radioactivity dose/kg of body weight.

Exploratory endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to standard-of-truth
- Comparison to sstr2 agonist results will be computed for sensitivity analysis
- Differences in SUV_{max} ratios between the two peptide mass dose ranges and three radioactivity dose ranges for lesions
- SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} between the three radioactivity doses.

For further details on efficacy endpoints, refer to the core study protocol and IRC.

Safety:

The investigator will report the occurrence of any AE throughout the study, including clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis), vital signs (blood pressure and heart rate) measurements, physical examination findings and body weight measurements at each visit: Screening Visit (Visit 1), Baseline Visit (Visit 2; Day 1), Visit 3 (Day 16 to Day 22), and End of Study/ Early Withdrawal Visit (Visit 4; Day 30 to Day 36). The electrocardiogram (ECG) findings are to be recorded at Screening Visit and End of Study/ Early Withdrawal (Visit 4; Day 30 to Day 36). Concomitant medications/therapies will also be recorded throughout the study.

The following safety endpoints will be evaluated:

- Proportion of subjects experiencing at least one AE of any grade according to NCI-CTCAE v5.0), including any SAEs and suspected unexpected serious adverse reactions (SUSARs); all AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (as per most recent version)
- Proportion of subjects experiencing at least one AE of grade ≥3 according to NCI-CTCAE
- Clinically significant changes in physical examination, vital signs, ECG and laboratory findings, which will be recorded by the investigator as AEs.

Pharmacokinetics:

- Characterization of the PK of OPS202:

OPS202 blood and urine PK sampling will be performed for all subjects participating in the study. Blood samples for measurement of OPS202 plasma levels will be collected at different time points at Visit 2 and Visit 3 (see Study Design – Assessments section). OPS202 plasma concentrations will be measured using a validated analytical method. Remaining plasma from the PK samples may be used to control the presence of potential major metabolites of OPS202. Urine collection to determine renal excretion of OPS202

will be performed over the first 6 hours in two separate samples (see Study Design – Assessments section).
Individual PK parameters of OPS202 (e.g., maximum observed drug concentration [C_{max}], area under the concentration time curve from time 0 to infinity [AUC_{∞}], etc.) will be computed using a non-compartmental approach.

Additional exploratory model-based analysis (population PK analysis) might also be conducted using NONMEM software.

Statistical methods:

Method of randomisation:

This study is randomised 1:1:1. Randomisation will be performed by variable blocks.

Sequences of Peptide Mass Doses and Radioactivity Doses

	Visit 2 (D1)	Visit 3 (between D16-D22)
Sequence A	5-20µg / 40-80 MBq	30-45µg / 100-140 MBq
Sequence B	5-20µg / 100-140 MBq	30-45µg / 160-200 MBq
Sequence C	5-20µg / 160-200 MBq	30-45µg / 40-80 MBq

A randomisation list will be prepared under the responsibility of the sponsor's biostatistics department. An appropriate randomisation system will be used allowing random allocation of the subjects per arm.

Sample size and power considerations:

It is anticipated that a total of 24 evaluable subjects will complete the study (i.e., receive two of the six combinations of dose ranges offered per protocol) and therefore to account for illegible or missing scans subjects with unacceptable scan images will be replaced in order to obtain at least 8 evaluable subjects in each study arm. To limit the extension of study duration if the last two potentially evaluable subjects (CCI [redacted]) should be non-evaluable, corresponding replacement subjects (randomisation number CCI [redacted], respectively) will be recruited as soon as possible. Therefore, a total of at least 25 subjects will be enrolled in the study to ensure the 48 PET scans for the analysis.

This is considered appropriate for a descriptive analysis and it is not based on formal statistical sample size calculation. In the event that a subject misses an imaging exam and/ or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited as a replacement to ensure an adequate sample size in the "per protocol set" for evaluation of overall lesions.

Statistical analysis

The combinations peptide/radioactivity dose ranges (see Methodology).

Each of the 24 evaluable subjects is to receive two different ^{68}Ga-OPS202 peptide/radioactivity dose range combinations. Hence, a total of 48 scans will be analysed (8 in each combination peptide/radioactivity dose range).

The number of scan sets generated will be as follows:

- All the 48 scans will serve for the primary and key secondary 2 × 3 factorial analysis endpoints
- 24 sets for each of the two peptide mass dose ranges regardless of the radioactivity dose which will be analysed to describe the difference between these two dose ranges
- 16 sets for each radioactivity dose range regardless of peptide mass dose, which will be analysed to describe the differences between these three dose ranges.

The analysis will be descriptive and no formal statistical tests are planned for the primary and secondary endpoints. Mean, standard deviation, median and ranges will be estimated.

The primary endpoint and secondary tumour-to-background ratio and SUV_{max} endpoints' analyses will be performed following the 2 × 3 factorial distribution of the imaging sets per combination of peptide/radioactivity dose ranges.

Overall differences among the three radioactivity doses, overall difference among the two peptide mass doses, and interaction between the peptide mass doses and radioactivity doses will be analysed.

Interim Analysis

An interim analysis will be performed when a minimum of 12 subjects have fully completed the study. The study will continue while the interim analysis is performed and the study may be stopped per sponsor's decision based on expert review of the data. The interim statistical analysis plan will provide further details of the statistical analyses.

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LIST OF ABBREVIATIONS

ABBREVIATION	*Wording Definition*
Ae	Cumulative amount of unchanged drug excreted into the urine
AE	Adverse event
ALARA	As low as reasonably achievable
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the [plasma/serum/whole blood] concentration time curve
AUC_{last}	area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration
$AUC_{0-\infty}$	Area under the [plasma/serum/whole blood] concentration time curve from time 0 to infinity
BMI	Body mass index
CA	Competent Authorities
CFR	Code of Federal Regulations
CL	Total plasma clearance
C_{max}	Maximum observed [plasma/serum/whole blood] drug concentration
CRO	Contract research organisation
CT	Computed tomography
D	Day
DICOM	Digital Imaging and Communications in Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eCRF	Electronic case report form
EU	European Union
EU-GMP	European Union Good Manufacturing Practices
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
^{68}Ga	Gallium – 68
^{68}Ga-DOTA-TATE	NETSPOT®

ABBREVIATION	*Wording Definition*
^{68}Ga-DOTA-TOC	Somakit-TOC
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GRPP	Good Radiopharmaceutical Practice
EANM	European Association of Nuclear Medicine
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
ICL	Imaging core lab
IEC	Independent ethics committee
IIP	Investigational Imaging Product
IND	Investigational New Drug
IRB	Institutional review board
IRC	Imaging review charter
i.v.	Intravenous
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
max	Maximum
MBq	Megabecquerel
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MeV	Mega electron-volt
min	Minimum
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NEC	Neuroendocrine carcinoma

ABBREVIATION	*Wording Definition*
NET	Neuroendocrine tumour
NOAEL	No observable adverse effect level
NODAGA	1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid
NOS	Not otherwise specified
PDM	Pharmacokinetics, Dynamics and Metabolism
PP	Per protocol
PET	Positron emission tomography
PK	Pharmacokinetics
PT	Preferred Term
QC	Quality control
RAP	Reporting and analysis plan
RBC	Red blood cell(s)
SAE	Serious adverse event
SAS®	Statistical Analysis System®
SD	Standard deviation
SNR	Signal-to-noise ratio
SOC	System organ class
SOP	Standard operating procedure
SPECT	Single-photon emission computed tomography
SSA	Somatostatin analogues
sstr	Somatostatin receptors
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardised uptake value
T½	Elimination half life
ULN	Upper limit of normal range
US(A)	United States (of America)
V	Volume of distribution
VOI	Volume of interest
WBC	White blood cell(s)
WHO	World Health Organisation
WHO-DD	World Health Organization (WHO) Drug Dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Neuroendocrine tumours are rare neoplasms [1, 2] with more than 50% of cases originating in the gastrointestinal (GI) system or pancreas [1]. Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) constitute a heterogeneous group of tumours with their origin in neuroendocrine cells of the embryological gut. Most commonly, the primary lesion is located in the gastric mucosa, the small and large intestine, the rectum or pancreas. The crude incidence has notably increased over the last decade and is estimated to be 5.25/100 000/year. The prevalence has recently been calculated to 35/100 000/year [3]. Importantly, approximately 80% of newly diagnosed patients present with metastasis, requiring an effective systemic treatment to prolong survival. The 5-year survival rate for this population is approximately 40% [4]. The latest World Health Organization (WHO) classification presented in 2010 defines the entire group of tumours as neuroendocrine neoplasms and divides the tumours into well differentiated NET G1, NET G2 and poorly differentiated neuroendocrine carcinoma (NEC G3) [5].

Most GEP-NETs overexpress somatostatin receptors (sstr), located on their cell surfaces [6]. To date a family of five different G protein-coupled sstr has been defined (sstr1–sstr5). The five subtypes share approximately half of the amino acid sequence, and have been shown to display different tumour tissue expression levels and biological functions. sstr2 is the most commonly expressed sstr in GEP-NETs (80-90%) [7].

The high expression level of sstr2 across the majority of tumours has led to the recommendation that for the clinical management, the initial disease staging should, whenever possible, include sstr scintigraphy which can nowadays be replaced by ^{68}Gallium-labelled agent positron emission tomography (PET) with very high spatial resolution and quantification. PET is recommended to be complemented with computed tomography (CT) or magnetic resonance imaging (MRI) depending on the tumour location [3].

Somatostatin-based radiolabeled agonistic peptides have been successfully introduced into the clinic for targeted imaging of sstr-positive NETs, especially of the clinically most relevant subtype sstr2. Currently three somatostatin-based radiolabeled peptide analogues are approved (or in Regulatory Authority review) in the US and/or Europe: namely, 111In pentetreotide (Octreoscan™), which is based on gamma rays, visualizing sstr-positive tumours in whole body single-photon emission computed tomography (SPECT) [8]; ^{68}Ga-DOTA-TATE (NETSPOT®) and ^{68}Ga-DOTA-TOC (Somakit-TOC) used with PET imaging that provides several advantages over SPECT such as temporal and spatial resolution, reduced radiation burden and diminished examination time [9, 10]. In addition, on site cyclotron technology is not required for ^{68}Gallium-labelled agents.

OPS202 is a new generation somatostatin analogue (antagonist) compound with potential superior tumour detection as a consequence of the availability of more binding sites, both active and inactive sstr2. It consists of the small somatostatin analogue JR11 conjugated to the strong cyclical chelating agent 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (NODAGA), which is radiolabelled with the radioactive isotope ^{68}Gallium to produce ^{68}Ga-OPS202. This complex (^{68}Ga-OPS202) is being developed as a PET imaging agent for the detection of GEP-NETs in patients.

^{68}Gallium is a short-lived (half-life 68 min) positron-emitting isotope generated from decay of the parent isotope ^{68}Germanium (half-life: 271 days). In the clinic, it can be created using a ^{68}Ga-generator. One of the main advantages of ^{68}Ga is its cyclotron-independent availability,

providing an inexpensive, decentralized and convenient alternative to cyclotron-generated isotopes. Furthermore, the non-halogenated nature and non-volatile chemical properties of ^{68}Ga characterize this isotope as an ideal PET tracer. Further key radiochemical characteristics of ^{68}Ga are summarised in Table 2.

Table 2 Radiochemical Characteristics of ^{68}Ga

^{68}Ga physical half-life $T_{1/2}$	Decay product	Maximum positron energy	Maximum linear range	Medium linear range
68 min	^{68}Zn	1.89 MeV	9.1 mm	1.9 mm

^{68}Ga-OPS202 as a PET radiopharmaceutical is a candidate being developed for integration in standard diagnostic tumour imaging.

In mice bearing sstr2-expressing tumours, ^{68}Ga-OPS202 showed a higher tumour uptake than the reference imaging radiopharmaceutical ^{68}Ga-DOTATATE (30.7±1.6 %IA/g versus 17.8±2.2 %IA/g, $p<0.05$ at 1 hour after injection), whereas tumour-to-kidney ratio was comparable for both radiolabelled peptides, suggesting a potential clinical benefit of the antagonist peptide ^{68}Ga-OPS202 over the agonist peptide ^{68}Ga-DOTA-TATE. Tumour-to-muscle ratio was in favour of ^{68}Ga-OPS202 as compared to ^{68}Ga-DOTA-TATE (153.5 versus 50.8 at 1 hour post-injection) as well as tumour-to-blood and tumour-to-liver ratios at 2 hours post-injection [11].

No relevant toxicological effect has been observed in OPS202 treated male and female rats for all investigated parameters (mortality, clinical signs, body weight, food consumption, clinical pathology, organ weights, macroscopic and microscopic examinations). The dose of 1.43 mg/kg OPS202 given once intravenously (i,v.) is within the no-observed-adverse-effect-level (NOAEL). Of note, the intended clinical mass dose administered to subjects is a maximum of 50 µg, which corresponds to 0.71 µg/kg for a 70-kg subject [11].

PPD

These imaging results encouraged further investigation of ^{68}Ga-OPS202 being a promising radiopharmaceutical tracer and potentially superior to the standard Octreoscan® or the newly approved ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-TOC in the diagnosis of GEP-NET lesions.

A single-centre, open-label, dose-finding, single-dosing study (Study OPS-B-001) was conducted to evaluate safety and tolerance, as well as biodistribution, dosimetry and preliminary efficacy of two single ^{68}Ga-OPS202 peptide mass doses (15±5 and 50±15 µg, each labelled with the same radioactivity dose 200 megabecquerels (MBq) ±25% of ^{68}Ga tracer (as initially described in the study protocol) for the diagnostic imaging of sstr2-positive GEP-NET using PET/CT.

Six out of 12 subjects (50.0%) experienced 11 adverse events (AEs), all of which were assessed by the investigator as being nonserious. Most of the AEs were mild in intensity and were considered by the investigator as unlikely or not related to the Investigational Imaging Product (IIP). Three AEs in two subjects were assessed as possibly related to ^{68}Ga-OPS202: eosinophilia, rash and diarrhoea. The most frequently reported AEs were urinary tract infection (n=2) and fatigue (n=2); these AEs were considered unlikely or not related to the IIP.

The study also showed promising preliminary efficacy results, with the most frequently identified lesions being malignant lesions in the liver. In all scans (somatostatin receptor 1-hour scan performed within 6 months before start of the study [pre-baseline] and the two ^{68}Ga-OPS202 dose 1-hour scans), malignant liver lesions were detected in nine subjects. Malignant lymph node lesions were identified in seven subjects in the pre-baseline somatostatin receptor 1-hour scan and eight subjects in the ^{68}Ga-OPS202 1-hour scans.

The detection rate of malignant lesions considering all organs/tissues (total) was significantly higher in the ^{68}Ga-OPS202 1-hour scans than in the pre-baseline somatostatin receptor 1-hour scan ($p \leq 0.016$). This was based on the significantly higher number of liver lesions detected in the ^{68}Ga-OPS202 1-hour scans compared to the somatostatin receptor 1-hour scan ($p \leq 0.012$). No significant difference was seen between the pre-baseline somatostatin receptor 1-hour scan and the ^{68}Ga-OPS202 1-hour scans with regard to the detection rate of malignant lymph node lesions.

1.2 Rationale to Conduct the Trial

The potential higher diagnostic accuracy of ^{68}Ga-OPS202 (satoreotide trizoxetan) PET/CT compared to pre-baseline somatostatin receptor scan warrants the progression of the compound into a phase II study to confirm the optimal dose, particularly as the analysis of the safety data of Study OPS-B-001 did not raise any concern.

The present dose-confirmation phase II study aims to define the optimal dose range for peptide mass and radioactivity based on detected number of lesions and tumour-to-background ratio in subjects with sstr2-positive GEP-NET. The study will also expand the evaluation of ^{68}Ga-OPS202 safety.

1.3 Population to Be Studied

The study will enrol adult subjects with sstr2-positive GEP-NET.

1.4 Peptide Mass Dose Rationale

In order to study the influence of specific activity (defined as radioactivity over peptide mass) on PET/CT image quality in the phase I/II clinical trial, two different peptide doses of 15 ± 5 µg and 50 ± 15 µg OPS202 (with ^{68}Ga activity of 125 to 195 MBq) were administered to the same patient at the first and the second visit, respectively, allowing intra-patient comparison and resulting in a range of specific activity of 3 to 13 MBq/µg. In the proposed phase II study, the peptide ranges are designed to cover the lowest achievable peptide dose (5 µg to 20 µg; close to the 15 ± 5 µg of the phase I/II) and the upper range, within the capability of the kit (30 µg to 45 µg; close to the 50 ±15 µg of the phase I/II).

The internationally recognized procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE, published by the European Association of Nuclear Medicine (EANM), which are based on the clinical experience with the known ^{68}Ga-labeled somatostatin receptor agonists, proposes use of less than 50 µg of (injected) peptide as this amount would be expected not to have clinically-significant pharmacological effect [12]. The present OPS202 kit-formulation is 50 µg

to ensure reliable radiolabeling with a ^{68}Ga radionuclide incorporation greater than 97%; the upper recommended limit of 50 µg was selected to compensate for the presence of potential metal contaminants (potential breakthrough of the parent radionuclide is possible [13] from the ^{68}Ge/^{68}Ga generator elution and to provide a margin for robust radiolabeling. In the formulation given to patients, approximately 0.01-0.04% of OPS202 is complexed to ^{68}Ga, whereas the remaining is unlabelled.

The OPS202 kit supplied to the investigator sites will have a total of 50 µg of peptide to be made up into a 6 mL solution with ^{68}Ga. A minimum of 0.5 mL or 4.2 µg of peptide will need to be withdrawn for quality control, leaving 5.5 mL or 45 µg of peptide available for injection. Based on this information, two peptide dose ranges were selected to be further evaluated in the phase II study: 5 µg to 20 µg and 30 µg to 45 µg, the latter value being the highest achievable from a 50 µg kit dose, as described above, and the lower dose is the lowest achievable that allows to adhere to the "as low as reasonably achievable" (ALARA) principle.

It is anticipated that a range of injected peptide mass doses provides greater flexibility for radioactivity dosing. It is of note that this flexibility is important in clinical practice since the radioactivity dose is influenced by the age of the gallium generator. Other factors like PET scanner characteristics and subject's body mass index (BMI) have to be accommodated by the flexibility in radioactivity dosing.

1.5 Radioactivity Dose Rationale

Three radioactivity dose ranges are proposed:

- 40 - 80 MBq
- 100-140 MBq
- 160-200 MBq

This phase II study will evaluate the radioactivity dose across a range that will be in the same order as the earlier phase I/II study with lower radioactivity doses also being evaluated to adhere to the ALARA principle. It is anticipated that to obtain good quality images with ^{68}Ga-OPS202 across a range of subject BMI and PET scanners, a radioactivity dose in the range of 100 MBq to 200 MBq will be required. To adhere to the ALARA principle and to identify a "near optimal dose" this phase II study will also evaluate a lower radioactivity dose range (40-80 MBq). It is anticipated that the lower radioactivity dose will be near optimal or below optimal for some subjects, particularly those who have a high BMI.

Therefore, the aim of this phase II study is to demonstrate that over the range of injected radioactivity dose of 100 MBq to 200 MBq there is a clear diagnostic signal, regardless of the injected peptide dose used. One can consider the peptide as the "^{68}Ga-carrier" that targets sstr2 receptors, and hence the peptide dose within the micro-dosing range selected should not be a factor in diagnostic efficacy, but adjusted to ensure optimal radioactivity dose reaches the target lesions.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

OPS202, an sstr2 antagonist compound, has demonstrated improved receptor binding, due to its capacity to bind both active and inactive sstr2, relative to sstr2 agonists. Therefore, the radiolabelled OPS202 potentially has an improved diagnostic performance as a PET imaging agent compared to ssrt2 agonists. Initial safety data have not raised any concerns. While the initial studies demonstrated good diagnostic performance in a single centre setting, the requirement to confirm both the peptide and radioactivity dose ranges in a multicentre setting was stipulated by the US Food and Drug Administration (FDA). This study will therefore be conducted to evaluate the optimal combination of peptide mass dose and radioactivity dose ranges to provide optimal diagnostic efficacy of ^{68}Ga-OPS202 for PET imaging in subjects with GEP-NET.

2.2 Study Objectives

The primary objective of the study is:

- To define the optimal dose range for peptide mass and radioactivity of ^{68}Ga-OPS202 based on detected lesions in adult subjects with sstr2-positive GEP-NET.

The secondary objectives of the study are as follows:

- To further refine the optimal dose range for peptide mass and radioactivity based on quantitative maximum standardised uptake value (SUV_{max}) and other image quality parameters
- To describe the safety and tolerability of diagnostic ^{68}Ga-OPS202 in subjects with sstr2-positive GEP-NET
- To characterize the pharmacokinetics (PK) of OPS202 in subjects with GEP-NET.

The exploratory objective of the study is:

- To provide preliminary estimates of the sensitivity of ^{68}Ga-OPS202 PET/CT scan imaging, as well as SUV ratio (SUV_{max} lesion/ SUV_{mean} reference tissue), signal-to-noise ratios (SNR).

3 STUDY DESIGN

Two target peptide mass dose ranges (5-20 µg and 30-45 µg), and three radioactivity dose ranges (40-80 MBq, 100-140 MBq and 160-200 MBq activity) of ^{68}Ga-OPS202 will be investigated to provide information on different possible peptide/radioactivity dose ranges combinations that are summarized in Table 3.

The IIP consists of a cold (OPS202) and a hot (^{68}Ga) component; the study will define the optimal dose by considering each of the two components. Approximately 0.02% of the total mass of the compound injected into the subject is hot.

Table 3 Combinations of Studied Peptide Mass dose Ranges and Radioactivity Dose Ranges

Peptide mass dose range	Radioactivity dose range		
	40-80 MBq	100-140 MBq	160-200 MBq
5 – 20 µg	8 scans	8 scans	8 scans
30 – 45 µg	8 scans	8 scans	8 scans

Each of the 24 evaluable subjects will receive two different peptide/radioactivity ranges combinations
Hence, 48 PET/CT scans will be analysed (8 in each combination peptide/radioactivity dose range)

3.1 General Design and Study Schema

This is a multicentre, multinational, randomised, open-label, reader-blinded, dose-confirmation, 2 × 3 factorial phase II study, with an approximate 7-week duration, to define the optimal dose range for peptide mass and radioactivity in subjects with sstr2-positive GEP-NET.

Subjects will be assigned to one of the three study arms (Figure 1). At the end of study, each subject will provide two sets of images corresponding to two combinations of peptide / radioactivity dose ranges. Each subject will have at least one radioactivity dose of 100 to 200 MBq.

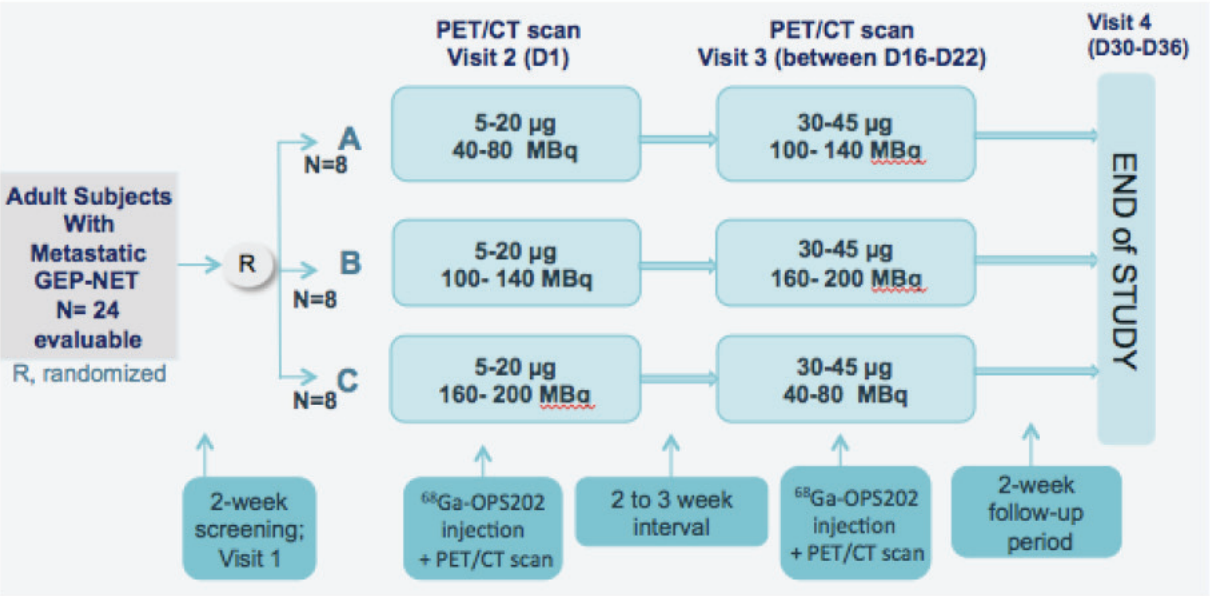

Figure 1 Study Design and Subjects Allocation

Subject participation in the study is estimated to last approximately 7 weeks and will include:

- Visit 1: A screening period up to 2 weeks
- Visit 2: A single intravenous (i.v.) injection of the first peptide/radioactivity dose of ^{68}Ga-OPS202 on Day 1 followed by PET/CT scan imaging 1 hour post dosing (up to 80 min)
- Visit 3: A single i.v. injection of the second peptide/radioactivity dose of ^{68}Ga-OPS202 followed by PET/CT scan imaging 1 hour post dosing (up to 80 min). This visit is scheduled 15 to 21days after the first ^{68}Ga-OPS202 administration (Visit 2)
- Visit 4: A 2-week follow-up period for evaluation of safety.

Screening Procedures (Visit 1)

During the Screening period (Visit 1) the investigator will select the candidate subjects and invite them to take part in the study. He or she will explain the study as indicated in Section 13.2 and obtain written informed consent before conducting any study procedure.

Randomisation and IIP Administration (Visit 2 and 3)

At Visit 2, eligible subjects will be randomised to one of the three study arms, to receive a single i.v. injection of ^{68}Ga-OPS202 with a peptide mass dose range of 5-20 µg and one of the radioactivity dose ranges (40-80 MBq, 100-140 MBq and 160-200 MBq activity of ^{68}Ga). After a time interval of 15 to 21 days (Visit 3), another single i.v. injection of ^{68}Ga-OPS202 will be administered to the subject with a peptide mass dose range of 30-45 µg and one of the radioactivity dose ranges (40-80 MBq, 100-140 MBq and 160-200 MBq activity of ^{68}Ga) according to the study scheme (Figure 1). Specific details of the dosage arms are given in Section 6.

Post Baseline Procedures (Visit 4)

Subjects who complete Visit 2 (first PET/CT scan) and Visit 3 (second PET/CT scan) will be considered to have completed the study for efficacy analysis.

Subjects who complete the study will have final procedures and assessments performed at the End of Study/Early Withdrawal Visit (Visit 4). Subjects who withdraw from the study before the completion of the second PET/CT scan evaluation will have Visit 4 (End of Study/Early Withdrawal Visit [Visit 4]) or early termination procedures and assessments performed at their final visit. An End of Study/Early Withdrawal Visit (Visit 4) will take place 2 weeks after the second PET/CT scan.

3.2 Primary and Secondary Endpoints and Evaluations

All the primary and secondary imaging endpoints are read by third party independent readers. Most of the reading will be conducted in a blinded manner.

3.2.1 Primary Efficacy Endpoint and Evaluation

- For each combination of injected peptide/radioactivity dose range, differences in relative lesion counts derived from a 2 × 3 factorial analysis measuring the ratio of the number of lesions detected by ^{68}Ga-OPS202 to the number of lesions assessed by standard-of-truth (descriptive analyses).

The standard-of-truth in this study is the CT scan images acquired at Visit 2 and Visit 3.

3.2.2 Secondary Efficacy Endpoints and Evaluations

Key Secondary Endpoint:

- For each combination of injected peptide/radioactivity dose range, differences in image quality derived from a 2 × 3 factorial analysis measuring the tumour-to-background ratio in each of the major anatomic sites (descriptive analyses for liver, lymph nodes, bone and lungs)

A qualitative analysis of the image assessed by the independent blinded readers will be performed to back up the quantitative quality measured by tumour-to-background analysis.

Other Secondary Endpoints:

- Differences in lesion SUV_{max} between the two peptide mass dose ranges and the three radioactivity dose ranges measured in the most avid lesions (descriptive analyses for up to a maximum of five lesions per organ in liver, lymph nodes, bone and lungs)
- Differences of absolute number of lesions between the two peptide mass dose ranges and the three radioactivity dose ranges detected in each of the following anatomic sites:
  - Primary site of GEP-NET
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
- The primary and secondary endpoints will also be evaluated on a radioactivity dose/kg of body weight.

Exploratory Endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to standard-of-truth
- Comparison to sstr2 agonist results will be computed for sensitivity analysis
- Differences in SUV_{max} ratios between the two peptide mass dose ranges and three radioactivity dose ranges for lesions
- SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} between the three radioactivity doses.

3.2.3 Safety Endpoints and Evaluations

The safety and tolerability of ^{68}Ga-OPS202 will be assessed throughout the study by evaluating AEs, clinical laboratory test results (serum chemistry, haematology, and urinalysis), vital signs measurements (blood pressure, heart rate and respiratory rate), electrocardiograms (ECGs), physical examination results and concomitant medication usage.

The following safety endpoints will be evaluated:

- Proportion of subjects experiencing at least one AE of any grade according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 5.0), including any serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)
- Proportion of subjects experiencing at least one AE of grade ≥3 according to NCI-CTCAE (version 5.0). All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (as per most recent version)
- Clinically significant changes in physical examination, vital signs, ECG and laboratory findings, which will be recorded by the investigator as AEs.

3.2.4 Pharmacokinetic Endpoints

OPS202 plasma concentration will be evaluated at the following timepoints: Baseline pre-dose (T0), 5 min, 15 to 45 min, 1h, 2h, 3h and 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits (Visit 2 and Visit 3). Urine collection to determine renal excretion of OPS202 will be performed over the first 6 hours in two separate samples: 0h to 3h and 3h to 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits (Visit 2 and Visit 3).

OPS202 PK parameters include the following:

- Maximum plasma concentration (C_{max})
- Area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration (AUC_{last})
- Area under the plasma concentration time curve extrapolated to infinity ($AUC_{0-\infty}$)
- Elimination half-life ($T_{1/2}$)
- Total plasma clearance (CL)
- Volume of distribution (V)
- Excreted amount of OPS202 in the urine over each time interval (see Section 3.2.4) as well as the 6-hour cumulative amount of unchanged OPS202 excreted into the urine (Ae).

3.3 Randomisation and Blinding

This is an open-label study and there is no blinding for the administration of the IIP nor for its doses (peptide mass dose as well as radioactivity dose).

An independent statistician (the sponsor's randomisation manager) will prepare the master list of randomisation numbers for this study. This list will be produced in blocks, on a balance ratio for the three sequences summarized in Table 4.

Table 4 Sequences of Peptide Mass Doses and Radioactivity Doses

	Visit 2 (D1)	**Visit 3 (between D16-D22)**
Sequence A	5-20µg / 40-80 MBq	30-45µg / 100-140 MBq
Sequence B	5-20µg / 100-140 MBq	30-45µg / 160-200 MBq
Sequence C	5-20µg / 160-200 MBq	30-45µg / 40-80 MBq

After eligibility is confirmed at Visit 2 (Day 1), subjects will be assigned to a randomisation number and to the associated sequence of study arm, in sequential order within each centre.

Each subject will receive, at Visit 2 and Visit 3, the peptide mass dose and radioactivity dose associated to this randomisation number. The randomisation number and the dose ranges will be provided by the electronic case report form (eCRF), which will assign the subjects in a study arm according to the predefined randomisation list. The investigator will under no circumstances be able to change the randomisation number and the sequence of treatment arms allocated to the subject.

Recruitment will stop once 24 evaluable subjects have been randomised and completed the study procedures. Each non-evaluable subject (see Section 3.6) will be replaced by a subject who will receive the same dose ranges sequence as the one assigned to the replaced subject. In this context, a mirror randomisation list will also be produced to randomise the replacement subjects. In this mirror randomisation list, only the replacement randomisation numbers of non-evaluable subjects will be considered.

The randomisation list will be produced for 24 randomisation numbers (from CCI) and for 24 replacement randomisation numbers (from CCI). For instance, the possible replacement randomisation number CCI will have to be used to randomise the possible replacement of subject who was randomised with randomisation number CCI

Randomised subjects who terminate their study participation for any reason before administration of the first dose of randomised study drug will retain their randomisation numbers (i.e. these numbers will not be reused). The next subject will be given another randomisation number, even if he/she should receive the same sequence of study arms.

Subjects who complete Visit 2 and do not complete the imaging of Visit 3 will be replaced. Also, if the images at Visit 2 or at Visit 3 are of unacceptable radiological quality (see Section 3.6), the subject will be replaced. Quality will be assessed by the imaging core lab (ICL) within 5 days of submission.

To limit the extension of study duration if the last two potentially evaluable subjects (randomisation numbers CCI) should be non-evaluable, corresponding replacement subjects (randomisation numbe CCI , respectively) will be recruited as soon as possible. If both potentially evaluable and replacement subjects are evaluable at the end of the study, the subjects assigned to randomisation numbers CCI will be included in the efficacy and safety analysis whereas the replacement subjects assigned to randomisation numbers CCI will be included only in the safety analysis. Therefore, a total of at least 25 subjects will be enrolled in the study to ensure the 48 PET scans for the analysis.

The sponsor's randomisation manager will keep the master randomisation lists. The master lists and the copy supplied to the contract research organisation (CRO) in charge of the eCRF and the ICL in charge of blinding of the imaging scans will be kept confidential in a secure location. Access to these randomisation lists must be restricted until authorisation is given to release them for final analysis.

3.4 Study Imaging Product and Dosage

The IIP is provided as a sterile two-vial radiolabelling kit constituted of freeze-dried powder containing 50 mg non-radiolabelled precursor OPS202 and excipients (Vial A) and the solvent for reconstitution (Vial B) to be used prior to radiolabelling.

The final radiolabelled IIP (^{68}Ga-OPS202) (one batch per kit and per subject dose) will be prepared in the local radiopharmacy at the clinical trial sites in a two-step aseptic compounding process:

- Reconstitution of the sterile vial A containing the OPS202 precursor and excipients with 1 mL of the solvent for reconstitution consisting of a solution of sterile sodium acetate from Vial B,
- Radiolabelling of the precursor OPS202 achieved by the addition of a 5 mL sterile hydrochloric acid solution of ^{68}Ga, eluted from a sterile pharmaceutical grade ^{68}Ge/^{68}Ga generator.

The test product, ^{68}Ga-OPS202, will be administered i.v. over one minute, at one of the doses shown in Table 3, and according to the randomisation of the subject.

A more detailed description of administration procedures is given in Section 6.1.1.

The investigators will receive a certificate of conformity and a certificate of analysis for each IIP batch. A Material Safety Data Sheet is also available.

The IIP packs and all vials will be labelled. Each label will be designed in accordance with Appendix 13 of the European Union Good Manufacturing Practices (EU-GMP) (see Appendix 1) and in accordance with specific local requirements if any. After reconstitution and radiolabelling the vial will be included in a lead container. This lead container will be labelled according to Appendix 13 of EU GMPs (see Appendix 1) and according to specific local requirements if any.

Final IIP reconstitution, radiolabelling, quality control (QC) and IIP release will be performed at the study site's radiopharmacy facility. Labels for the final IIP and containers can be provided by the sponsor if required by the clinical site.

The IIP (OPS202, cold precursor) will be packaged and delivered to the investigational sites/central or interim storage facilities. A sufficient quantity of IIP will be supplied as well as an acknowledgement of receipt form. No code break envelopes will be supplied as the double blinding relates to the independent central readers.

The investigator, or designee, will only administer IIPs to subjects included in this study. Each subject will only be given the IIP carrying his/her number. The dispensing by the responsible pharmacist and the administration to each subject will be documented in the eCRF.

The peptide mass dose ranges and the radioactivity dose ranges are summarized in Table 3, and their sequence of administration in Figure 1.

3.5 Study Duration

This study will consist of up to a 2-week screening period, an approximately 3-week imaging period, and a 2-week follow-up period. Subjects are expected to participate in this study for a minimum of 6 weeks and up to 7 weeks.

The subject's participation in the study will be considered to have ended at the time of the last visit (Visit 4 or End of Study/Early Withdrawal Visit), which should occur approximately 2 weeks after their last IIP administration.

3.6 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1.3) as they are reported from the study centres to identify safety concerns. The study may be terminated by the sponsor at any time.

A subject may discontinue participation in the study at any time for any reason (e.g., withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g., protocol deviation as defined in Section 12.1.2, noncompliance with the protocol conditions or AE).

If a subject's Visit 2 ^{68}Ga-OPS202 PET/CT scan images are non-evaluable for whatever reason, the subject will be discontinued from the study. This study has a small number of subjects requiring two timepoints for image evaluation.

Each non-evaluable subject will be replaced by a subject who will receive the same IIP sequence as the one assigned to the replaced subject (see Section 3.3). A non-evaluable subject is one for whom any of the following image sets are missing or of unacceptable quality for ICL:

1) Visit 2 and/or Visit 3 ^{68}Ga-OPS202 PET/CT scans, as these provide the "standard-of-truth" information and both are needed for the factorial design
2) Previous somatostatin receptor scans, which confirm the presence of sstr2 in the tumour

3) All images will be reviewed and assessed by ICL to ensure there are no quality issues relating to artefacts that are detrimental to the study endpoints. These primarily consist of the following:
    (a) Metal implants
    (b) Patient motion
    (c) Excessive breathing artefacts between the PET and CT scan images.

3.7 Investigational Imaging Product Preparation, Storage and Accountability

3.7.1 Investigational Imaging Product Storage and Security

The investigator, or an approved representative (e.g., pharmacist), will ensure that all IIP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

3.7.2 Investigational Imaging Product Preparation

The investigator, or an approved representative (e.g., pharmacist), will ensure that all IIP is reconstituted, radiolabelled and dispensed by qualified staff members in order to be administered to the subject.

3.7.3 Investigational Imaging Product Accountability

All IIP and any other study related material is to be accounted for on the IIP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The investigator should ensure adequate records are maintained in the IIP accountability log.

The destruction of used and unused study treatment should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. The study treatment will be destroyed on site.

3.8 Maintenance of Randomisation and Blinding

This is an open-label study; there is no blinding for the imaging product used nor for its doses (peptide mas dose as well as radioactivity dose). The scan images collected at Visit 2 and Visit 3 are to be read centrally in a blinded manner.

The images will be sent to a central imaging core lab ICL. The ICL will ensure that the ^{68}Ga-OPS202 and CT images are initially presented to the readers in a blinded manner and randomised to temporal sequence. Blinding includes subject ID, site, type of scanner(s), peptide mass dose and radiation dose (and therefore visit number). Full details of this complex read will be provided in the Imaging Review Charter (IRC).

3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 Code of Federal Regulations (CFR) Part 11. As required by Good Clinical Practice (GCP), the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IIP administration, and any AEs and associated concomitant medication.

As required by International Conference on Harmonisation (ICH GCP) Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definition for source data and source documents are given below:

- **Source Data**: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source Documents**: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files, and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study). The results of the independent central read are also considered source documents.

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local, and possibly foreign, competent authorities (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

All subjects must fulfil all the following criteria to be included in the study:

1) Men or women aged 18 years or older
2) Subjects with pathologically confirmed, well differentiated functioning or non-functioning metastatic GEP-NET (Grade I and II as per WHO classification 2010)
3) Subjects with a confirmed presence of somatostatin receptors (type 2) on technically evaluable tumour lesions documented by a positive Somatostatin Receptor Scan acquired within 6 months prior to screening (Visit 1) and showing minimally two lesions in at least one of the key organs (liver, lymph nodes, bone and lungs); these images shall be available to be sent to the ICL electronically to ascertain quality and admissibility
4) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
5) Subjects with body weight between 50 kg (110 lb) and 110 kg (243 lb), inclusive
6) Adequate bone marrow, liver and renal function, with:

- Calculated Glomerular filtration rate (GFR) ≥ 45 mL/min
- Albumin: > 30 g/L
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP): ≤ 5 times upper limit of normal (ULN)
- Bilirubin: ≤ 3 times ULN (3 × 1.1 mg/dL)
- Leukocytes: ≥ $3*10^9$/L and neutrophils ≥ $1*10^9$/L
- Erythrocytes: ≥ $3.5*10^{12}$/L
- Platelets: ≥ $90*10^9$/L

7) Signed written informed consent prior to any study-related procedures

4.2 Exclusion Criteria

Subjects will not be eligible for inclusion in the study if they have any of the following:

1) Subjects with fewer than five lesions in total and more than 25 lesions/organ detected by the somatostatin receptor positive scan in key organs: liver, lymph nodes, bone or lungs
2) Subject who have received treatment of any somatostatin analogue, including Somatuline® Autogel® /Depot®, Sandostatin® LAR within 28 days, and Sandostatin® within 24 hours prior to first ^{68}Ga-OPS202 administration.
3) Presence of active infection at screening or history of serious infection within the previous 6 weeks prior to the first ^{68}Ga-OPS202 administration
4) Prior or planned administration of a radiopharmaceutical within 8 half-lives of the radionuclide
5) Clinically relevant trauma within 2 weeks prior to first ^{68}Ga-OPS202 administration
6) Known hypersensitivity to NODAGA, to Gallium-68, to JR11 or to any of the excipients of ^{68}Ga-OPS202
7) History of, or current active allergic or autoimmune disease, including asthma or any condition requiring long-term use of systemic corticosteroids
8) Known human immunodeficiency virus (HIV) or positive serology for HIV, hepatitis B and C

9) Any condition that precludes the proper performance of PET and/or CT scan:
- Subjects who are not able to tolerate the CT contrast agent,
- Subjects with metal implants or arthroplasty, or any other objects that might interfere with the PET and/or CT analysis
- Subjects unable to raise arms for prolonged imaging purposes
- Subjects unable to lie still for the entire imaging time
- Subjects weighing greater than 110 kg (243 lb)

10) Administration of another investigational medicinal product within 30 days prior to first ^{68}Ga-OPS202 administration

11) Female subjects who are pregnant, breast feeding or of childbearing potential not willing to practice effective contraceptive techniques during the study treatment period and for 30 days after the last dose of ^{68}Ga-OPS202 administration; pregnancy test must be performed at the start of the study and prior to each ^{68}Ga-OPS202 administration

12) Subjects who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, including any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude

13) Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus and/or subjects treated with curative intent and free from disease for more than 5 years) other than NET

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. Any subject who becomes pregnant during the course of the study will be withdrawn (see Sections 8.1.4 and 8.2.4). In addition, a subject may be withdrawn from the study as described in Sections 3.6, 5.2.4.1, 6.2 and 8.1.6.

Should a subject decide to withdraw from the study after administration of IIP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.4.1) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the IIP or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the subject receives IIP, or as soon as possible thereafter.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 5.

Table 5 Study Procedures and Assessments

Study Visits [1]	Screening Visit 1	Day 1 Visit 2*	Day 16-22 Visit 3*	End of Study/Early Withdrawal visit Day 30-36 Visit 4
Informed consent [2]	X			
Inclusion/exclusion criteria	X	X		
Randomisation		X		
Demographics [3]	X			
Medical history [4]	X			
Prior therapies [4]	X			
Concomitant therapies [5]	X	X	X	X
Physical examination [6]	X	X	X	X
Vital signs [6]	X	X	X	X
ECG [7]	X			X
Haematology [8]	X	X	X	X
Blood chemistry [9]	X	X	X	X
Blood PK sampling [10]		X	X	
Urinalysis [11]	X	X	X	X
Urine PK sampling [12]		X	X	
Pregnancy test [13]	ßHCG (blood test)	Urinary hCG	Urinary hCG	ßHCG (blood test)
Somatostatin Receptor Scan [14]	X			
^{68}Ga-OPS202 PET/CT imaging [15]		X	X	
Adverse events [16]	X	X	X	X
Compliance [17]		X	X	

[1] **Study visits**: Screening Visit up to 2 weeks; Visit 3 will occur between Day 16 and Day 22, Follow-up Visit to be performed 2 weeks after Visit 3. * The subjects may be hospitalised overnight at Visit 2 and Visit 3 at the discretion of the investigator. On Day 2 (prior to discharge if subject hospitalised), the subject should undergo the following examinations: review of AEs, new or changed concomitant medications, vital signs, physical examination, haematology, biochemistry, urinalysis.

[2] **Informed consent**: Must be obtained prior to undergoing any study specific procedures and may occur prior to the 2-week screening period

[3] **Demographics**: Age, sex and self-reported race/ethnicity

[4] **Medical history and prior therapies**: To include clinically significant diseases, surgeries, cancer history (including prior NET Therapies) and all relevant medications

[5] **Concomitant medications**: Dose and indication will be recorded from 3 months prior to the start of study treatment, at study entry and at each visit. Once the subject has withdrawn from the study, concomitant medications and treatments should be recorded until all study treatment-related toxicities have resolved;

[6] **Physical examination**: Major body systems, body weight, height (screening visit only), vital signs 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure, heart rate), body temperature, respiratory rate

[7] **ECG**: Twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured automatically as per study site usual practice. The ECG will be recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available

[8] **Haematology**: Red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) absolute count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count

[9] **Blood chemistry**: urea, creatinine, chloride, bicarbonate, sodium, potassium, calcium, phosphate, total bilirubin, conjugated bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose

[10] **Blood PK Sampling**: Blood samples of 2 mL will be collected at the following timepoints: Baseline pre-dose (T0), 5 min, 15 to 45 min, 1h, 2h, 3h and 6h after the ^{68}Ga-OPS202 intravenous administration

[11] **Urinalysis**: Dipstick for pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocyte esterase, glucose and specific gravity

[12] **Urine OPS202 measurement**: Urine collection during the 6 hours post-dosing: in two separate samples: 0h to 3h and 3h to 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits (Visit 2 and Visit 3); subject will be asked to empty his/her bladder before dosing

[13] **Pregnancy test:** A pregnancy test will be performed at each visit particularly before each ^{68}Ga-OPS202 administration.

[14] **Somatostatin Receptor Positive Scan**: Results available in the preceding 6 months to the first administration of ^{68}Ga-OPS202 PET. Anonymized Images to be sent to the Imaging Core Lab

[15] **^{68}Ga-OPS202 PET/CT imaging**: Anonymized images to be sent to the Imaging Core Lab; i.v. iodinated CT contrast is required and will be injected according to the site standard procedure.

[16] **Adverse events**: Subjects must be followed for AEs, regardless of relationship, from the time they signed the informed consent until at least 14 days after the last dose of investigational imaging product (IIP). Clinically significant changes in physical examination, vital signs, electrocardiogram and laboratory findings will be recorded as an adverse event

[17] **Compliance**: The dose injected will be recorded at each visit.

5.2 Study Visits

5.2.1 Procedures for Screening and Enrolment (Visit 1)

A signed and dated informed consent form will be obtained before screening procedures begin. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study-specific evaluations. Subjects will be asked to acknowledge and agree to the possible use of this information for the study by giving informed consent.

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

The Screening visit (Visit 1) will take place within the 2-week period prior to randomisation. The following assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Demographic data (date of birth/age, sex and race/ethnicity will be collected according to individual country regulations/requirements). The collection of these data is needed to establish whether or not there are potentially clinically important sex- and racial/ethnic-based differences in the anticipated effects of the studied product.
- Medical history, including ongoing medical history
- Physical examination

- Vital signs (supine and standing blood pressure, heart rate and respiratory rate)
- ECG
- Body temperature
- Body weight
- Body height
- Laboratory safety tests (blood sampling for haematology and biochemistry, and urinalysis)
- Beta human chorionic gonadotropin (ß-HCG) pregnancy test for women of childbearing potential
- Prior and concomitant medications/therapies; please record the time period of concomitant medication(s) before subject begins the study
- Prior and concomitant nondrug therapies and surgical procedures
- Collection of AEs after signed informed consent has been obtained
- Collection of previous somatostatin receptor scan and send to ICL.

Each investigator will also maintain a record of all subjects screened into the study (i.e., who signed the informed consent form). Records up to the time of premature termination should be completed. In the event that the subject did not receive IIP, the primary reason will be recorded.

5.2.2 Procedures Before Study IIP administration (Baseline/Visit 2 and Visit 3 Predose)

The following procedures will be performed at Baseline/Day 1 (Visit 2) and at Day 16-22 (Visit 3) of the study, prior to the administration of IIP and information recorded (pre-dosing):

- Eligibility confirmation, which applies that any test results needed for this check should be already available (some exams/tests may be repeated if not available from the Screening Visit or are clinically and medically needed before ^{68}Ga-OPS202 administration)
- Following confirmation of eligibility for the study, subjects will be given a randomisation allocation number and allocated to one of the three study arms specified in Section 6.1.
- Review of AEs that may have occurred since informed consent form signature and before the first administration of the IIP (Visit 2)
- Review of AEs that may have occurred before the second administration of the IIP (Visit 3)
- Investigator will ensure that the subject can safely receive ^{68}Ga-OPS202 and the PET scan can be performed. For women of potential childbearing age, the results of urinary pregnancy test (test strips provided by central laboratory) should be obtained before ^{68}Ga-OPS202 administration.
- Pregnancy test on urine specimen (test strips provided by central laboratory) for women of childbearing potential.

If the subject continues to meet all eligibility criteria at Visit 2, he/she will receive a single injection of ^{68}Ga-OPS202 as per randomised allocation to one of the three study arms and will undergo PET/CT imaging.

N.B. For Visit 2 and Visit 3, subjects may be required to be hospitalised overnight at the discretion of the investigator.

5.2.3 Procedures During Study Treatment (Visit 2 and Visit 3 - Postdose)

The following procedures will be performed at Visit 2 (Day 1), and Visit 3 (Day 16 to 22)]:

- Review of AEs
- New or changed concomitant medications
- Vital signs at 0.5h, 1h, 2h and 4h post-injection
- Whole body PET/CT images will be acquired 1 hour (static) after ^{68}Ga-OPS202 injection (up to 80 min); i.v. iodinated CT contrast is required and will be injected according to the site standard procedure.
- PK assessments of OPS202:
  - Blood sampling will be performed at Baseline pre-dose (T0), 5 min, 15 to 45 min, 1h, 2h, 3h and 6h after the ^{68}Ga-OPS202 i.v. administration for both doses at the corresponding visits (Visit 2 and Visit 3)
  - Urine collection to determine renal excretion of OPS202 will be performed over the first 6 hours in two separate samples: 0h to 3h and 3h to 6h. Subject will be asked to empty his/her bladder just before the ^{68}Ga-OPS202 i.v. administration and then all urine voided during each of the above-mentioned time intervals will be collected and stored.

The subject may be hospitalised overnight at the discretion of the investigator. On the next day (Day 2), the Investigator will evaluate if the subject is fit to be discharged home. Subjects who are not hospitalised have to return to the investigator site the next day (Day 2). Prior to discharge, the subject should undergo the following examinations, for which the results must be recorded on the eCRF:

- Review of AEs
- New or changed concomitant medications
- Vital signs (supine and standing blood pressure, heart rate and respiratory rate)
- Physical examination
- Body weight
- Clinical laboratory tests (blood sampling for haematology and biochemistry, and urinalysis)

Upon discharge from hospital on Visit 2 (Day 2), the subject will be asked to return to study site in order to receive the next dose level (within 15 to 21 days). Upon discharge from the hospital on Visit 3 (Day 17 – Day 23), the subject will be asked to return to the study site in two weeks for safety follow-up.

5.2.4 Procedures After Study Imaging Agent Administration

Two weeks after the second ^{68}Ga-OPS202 PET/CT scan, the subject will come back to the study site for Visit 4 (End of Study/Early Withdrawal Visit).

5.2.4.1 End of Study Visit (Visit 4) or Early Withdrawal Visit

Subjects who participate in the study in compliance with the protocol for the two IIP administrations (at Visit 2 and Visit 3) will be considered to have fully completed the study for efficacy analysis. Those who in addition attend End of Study Visit (Visit 4) will be considered to have fully completed the study (i.e., efficacy and safety).

For subjects who complete the study, or for those who withdraw prematurely from the study (see Section 4.3), final evaluations will be performed approximately two weeks after the subject

receives the IIP. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.2 and Section 8.1.1.4, respectively.

The following procedures will be performed at the End of Study (Visit 4, Day 30 to Day 36), or Early Withdrawal Visit:

- Review of AEs
- New or changed concomitant medications
- Physical examination
- Vital signs (supine and standing blood pressure, heart rate and respiratory rate)
- ECG
- Body temperature
- Body weight
- Laboratory safety tests (blood sampling for haematology and biochemistry, and urinalysis)
- ß-HCG pregnancy test for women of childbearing potential

6 DIAGNOSTIC IMAGING OF SUBJECTS

6.1 Study Imaging Product

6.1.1 ^{68}Ga-OPS202

At Screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be randomised to one of the following sequence of ^{68}Ga-OPS202 peptide mass dose/ radioactivity dose ranges:

- Arm A: 5-20 µg/ 40-80 MBq at Visit 2 and 30-45 µg/ 100-140 MBq at Visit 3

or

- Arm B: 5-20 µg/ 100-140 MBq at Visit 2 and 30-45 µg/ 160-200 MBq at Visit 3

or

- Arm C: 5-20 µg/ 160-200 MBq at Visit 2 and 30-45 µg/ 40-80 MBq at Visit 3

^{68}Ga-OPS202 is a diagnostic medicinal product with three main components, namely:

- ^{68}Ga, a positron emitter radionuclide with a half-life of 68 min
- NODAGA, a chemical chelator group, and
- JR11, an antagonist somatostatin analogue that binds to sst2 receptors

OPS202 (cold kit) is available for clinical trials in a 50 µg peptide dose vial, and is radiolabeled using a ^{68}Ge/ ^{68}Ga-generator. Due to the short half-life (68 min) of the ^{68}Ga radioisotope, on-site generation of ^{68}Ga-labeled radiopharmaceuticals is mandatory. The ^{68}Ga is eluted initially from the generator with hydrochloric acid and the eluate combined with the reconstituted peptide kit preparation. The radiolabelling occurs at room temperature. The product then undergoes radiopharmaceutical quality control (see Preparation, Radiolabeling and QC manual).

The radiolabelled OPS202 (^{68}Ga-OPS202) consists of 50 µg of peptide in a total volume of 6 mL (8.33 µg/mL). Sampling of 0.5 mL for QC yields 5.5 mL solution from which the volume to be administered is withdrawn. This volume to be injected is calculated to obtain the target peptide mass dose and the desired radioactivity dose.

The calculation of the volume takes into account the different components that determine the final radioactivity dose, the subject will be exposed to, in particular:

- The amount of ^{68}Ga eluted from the generator which depends on the latter half-life
- The time elapsed between OPS202 (cold kit) radiolabelling and the injection of ^{68}Ga-OPS202 to the subject (decay of ^{68}Ga), the variation of which is a tool to adjust the final peptide/radioactivity dose required to be injected
- The required peptide mass dose and radioactivity dose of ^{68}Ga-OPS202 to be injected.

The actual peptide mass dose administered to the subject (injected dose) will be estimated using the following equation:

Injected dose (µg) = [Volume injected (mL) / Volume used for ^{68}Ga-OPS202 preparation (mL)] x Peptide dosage in the vial (µg) = [Injected Volume/6mL] x 50µg

The radioactivity in the syringe is measured immediately before the injection of ^{68}Ga-OPS202 to the subject and immediately after; the difference between these two measurements (in MBq) constitutes the radioactivity dose injected to subject.

^{68}Ga-OPS202 will be administered twice during the study for each subject by i.v. injection over one minute. After injection is completed, any remaining imaging agent in the cannula is rinsed,

when appropriate, with 10 mL normal saline (0.9 % NaCl solution). The PET/CT scanner must be the same for the two scans per subject and for all subjects at the same study site.

There are no fasting conditions, nor food restrictions that should apply when administering ^{68}Ga-OPS202 to the subject. N.B.: ^{68}Ga-OPS202 is labelled according to Good Radiopharmaceutical Practice (GRPP) per EANM guidelines and according to national regulations on radiopharmaceuticals. The radiopharmacy will receive training and specific written instructions on the labelling procedure.

Radiation dose:

According to data published for fluorodeoxyglucose (FDG) PET the effective dose was 6.23 mSv [14]. Doses from FDG PET scanning to the gonads, uterus, and bladder were higher than to the other organs and were 5.0, 7.8, and 59.2 mSv, respectively. This is because of the final accumulation of 18F in the bladder. Other organ doses ranged from 2.5 to 4.8 mSv. The total effective doses of the combined PET/CT studies, calculated by summing the effective doses of CT and PET scanning ranged from 13.45 to 31.91 mSv for female patients and 13.65 to 32.18 mSv for male patients taking various CT protocols into consideration [14]. Average contrast-enhanced CT of abdomen and pelvis dose is 20 mSv [15].

In the phase I/II study ^{68}Ga-OPS202, the calculated effective dose for an injection of 150 MBq (4 mCi) of ^{68}Ga-OPS202 was 3.6 mSv, which is lower than the radioactivity dose of the FDA- and EMA-approved Octreoscan^{TM}.

In this trial, each subject will get two PET/CT examinations with a 2- to 3-week interval between the two examinations. The total ^{68}Ga-OPS202 in each 3-study arm will range from 140 to 340 MBq (calculated by summing the doses at Visit 2 and Visit 3). Based on phase I/II study, the total dose for the study will range from approximately 3.6 mSv to 7.5 mSv. The dose of two CTs will depend on the imaging protocols and will not exceed 20 mSv for each CT examination. Thus, total cumulative dose for two PET/CT examinations will range from approximately 44 to 48 mSv.

6.1.1.1 Spillage

All due precautions and site procedures should be implemented to prevent spillage or leakage of radiodiagnostics. Infusion bags, intravenous lines, venous access should all be secured and the connections thoroughly checked. The infusion line should be taped in a loop and taped to the subject to prevent direct tension between the line and the venous access.

Despite precautions, if spillage or leakage should occur, then the site procedures must be implemented to protect the subject, staff and members of the public from radiation exposure. The subject should be moved from the area of the spillage or leakage while the area is decontaminated. Details of the spillage or leakage should be recorded (including how the incident happened, the time of the incident, an estimate (if possible) of the amount of substance lost) and the measures taken. In addition, the incident is to be reported in the same manner as an adverse event using the MedDRA PT Product Leakage and as appropriate PT Occupational exposure to radiation (if there is exposure to staff) and PT Exposure to radiation (if there is exposure to the subject or members of the public).

6.1.2 Other Investigational Medicinal Products

There are no investigational products other than ^{68}Ga-OPS202 in this study.

6.1.3 Other Study Drugs

Not applicable.

6.2 Concomitant Medication/Therapy

Any relevant prior or concomitant therapy or medication given to a subject within 3 months before IIP administration, during IIP administration and up to the end of the follow-up period will be indicated on the eCRF. Dose and generic name or tradename will be recorded.

The following concomitant medications /therapies are not permitted during this study up to the second PET/CT scan and 48 hours post second OPS202 scan:

- Administration of any radiopharmaceutical
- On Visit 2 and Visit 3 parenteral amino acid solutions and any formulation of diuretics are not allowed. Stable adjusted diuretics such as for subjects with hypertension are permitted.

Long acting SSAs, ie, Somatuline® Autogel® /Depot® (60, 90 or 120 mg) and Sandostatin® LAR (20 or 30 mg) will not be allowed within 28 days prior to the first ^{68}Ga-OPS202 PET/CT exam (at Visit 2) and during the study up to Visit 3 after the second ^{68}Ga-OPS202 PET/CT exam has been completed. Short acting Sandostatin® is allowed during the study with a washout period of 24 hours before each of the two ^{68}Ga-OPS202 PET/CT (Visit 2 and Visit 3), to avoid possible interaction between the non-radioactive SSA and OPS202.

Subjects on long acting SSA who need to continue such treatment for symptom control, should be switched to short acting SSA with a 24 hour wash out period before each of the two ^{68}Ga-OPS202 PET/CT (Visit 2 and Visit 3). Long acting SSAs can be resumed after Visit 3.

Other concomitant medications are permitted during this study at the discretion of the investigator but they must be monitored closely and every effort should be made to keep their dose and dose regimen constant throughout the course of the study.

6.3 Procedures for Monitoring Subject Compliance

The IIP is administered i.v. by the investigator or his/her delegate. Therefore, no specific procedure is required for monitoring subject compliance. The injected peptide mass dose and radioactivity dose will be recorded in the medical file and in the eCRF for each subject.

The investigator will ensure that the subject did not and is not taking any of the prohibited medication listed in Section 6.2 during the study period.

7 ASSESSMENT OF EFFICACY

For the timing of efficacy assessments in this study, refer to the schedule in Table 5.

The sets of images obtained at Visit 2 and Visit 3 for the primary endpoint and most of the secondary endpoint analyses will be sent to an ICL for centralised blinded reading by two independent experienced radiologists/nuclear medicine physicians, and a third for adjudication of discordances. The readers will be specifically trained for this protocol. Full details of the read design and conduct will be provided in the IRC.

For the primary endpoint analysis, the number of lesions on each subject scan will be counted on a per organ basis by the two primary independent readers. Scans will be blinded to subject, site, peptide and radioactivity dose. In case of discrepancy, images will go to the adjudicator (third reader) for a final read and adjudication.

After blinded reading, the readers will compare the paired scan for each subject and note which of the pair provides superior images based on overall image quality and lesion count.

The primary endpoint is the mean number of lesions identified in each tabular cell (see Table 3) as the ratio of the maximum number of lesions identified per organ per subject, removing individually differing absolute lesion numbers as a confounder and allowing the factorial design to be established to identify the optimum peptide mass and radioactivity dose.

The sequence of image display and recording of results will be as follows on a per subject basis:

1) Review of the two image sets of ^{68}Ga-OPS202 scans in randomised step-wise fashion, without and with CT image fusion. The PET and CT images acquired at the same time will be used for co-registration.
2) CT images for standard-of-truth assessments will be reviewed by two radiologists not involved in PET/CT images read. It is not anticipated that there will be a difference in the lesion counts between the two visits related to disease progression, due to slow development of GEP-NETs; however, there may be technical reasons for variations between the scans
3) Review of the lesion-to-background ratios in each major anatomical site (liver, lymph nodes, bone and lungs) based on the evaluation of up to five most avid lesions per organ
4) SUV_{max} calculations of the five most avid lesions per organ on PET scans (liver, lymph nodes, bone and lungs)
5) For image quality, direct comparison of the two ^{68}Ga-OPS202 scans with different peptide and radioactivity doses
6) Evaluation of previously acquired ssrt2 receptor agonist positive scans.

7.1 Primary Efficacy Endpoint and Evaluation

For each combination of injected peptide/radioactivity dose ranges, differences in relative lesion counts derived from a 2 × 3 factorial analysis measuring the ratio of the number of lesions detected by ^{68}Ga-OPS202 to the number of lesions assessed by standard-of-truth: blinded read-out (derived from above recording of results, points 1 and 2) with descriptive analyses.

7.2 Secondary Efficacy Endpoints and Evaluations

Key Secondary Endpoint:

- For each combination of injected peptide/radioactivity dose ranges, differences in image quality derived from a 2 × 3 factorial analysis measuring the tumour-to-background ratio in each of the major anatomic sites (descriptive analyses for liver, lymph nodes, bone and lungs)

A qualitative analysis of the image quality as assessed by the blinded readers will be performed to back up the quantitative quality measured by tumour-to-background analysis.

For further details, refer to the IRC.

Other Secondary Endpoints:

- Differences of lesion SUV_{max} between the two peptide mass dose ranges and the three radioactivity dose ranges measured in the most avid lesions: descriptive analyses for up to a maximum of five lesions per organ (derived from above recording of results, point 4), in liver, lymph nodes, bone and lungs
- Differences of absolute number of lesions between the two peptide mass dose ranges and the three radioactivity dose ranges detected in each of the following anatomic sites, both as standalone and also compared to the standard-of-truth scans; blinded read-out (derived from above recording of results, points 1 and 2) with descriptive analyses:
  - Primary site of GEP-NET
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
- The primary and secondary endpoints will also be evaluated on a radioactivity dose/kg of body weight.

Exploratory Endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to standard-of-truth
- Comparison to sstr2 agonist positive scan results will be computed for sensitivity analysis
- Differences in SUV_{max} ratios between the two peptide mass dose ranges and three radioactivity dose ranges for lesions.
- SNR calculated from lesion-free VOI in the liver: SUV_{mean}/SUV_{SD} between the three radioactivity doses.

For further details on efficacy secondary endpoints assessment, refer to the IRC.

7.3 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

Methods for assessing efficacy data are listed below and are described in further detail in the IRC. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1, and methods of analyses are discussed in Section 10.4.5.

All images will be sent to a central ICL for QC and central read management. This comprises the following images:

- Prior sstr2 agonist positive PET scans (see Section 4.1)
- All ^{68}Ga-OPS202 PET/CT scans.

The details of imaging set management and read design will be fully described in the IRC. This will include the following:

- Full acquisition guidelines for the site
- Process for PET scanner quality control (phantom assessments and reporting)
- Image transmission methodology

- Core lab QC methodology and management of the images
- Read design for primary endpoint
- Read design for secondary endpoint and process for calculating tumour-to-background ratio and SUV_{max}
- Design of exploratory endpoints
- Conduct of the read
- Management, training and inter-reader evaluation
- Data management
- Data export overview
- Archiving of images.

8 ASSESSMENT OF SAFETY

The safety and tolerability of ^{68}Ga-OPS202 consists of evaluating:

- AEs throughout the study
- Clinical laboratory test results (serum chemistry, haematology, urinalysis) throughout the study
- Vital signs measurements (blood pressure and heart rate) throughout the study
- ECG at Visit 1 and 4 (End of treatment/ Early Withdrawal)
- Physical examination results throughout the study
- Concomitant medication usage throughout the study.

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.1.

Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IIP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).

8.1.1 Categorisation of Adverse Events

8.1.1.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the NCI-CTCAE (version 5.0). In view of meta-analyses, and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,
- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe**: symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.

- **Life threatening**: any event that places the subject at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.3).

8.1.1.2 Causality Classification

The relationship of an AE to IIP administration will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IIP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IIP administration.

8.1.1.3 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the IIP IB.

The reference document for assessing expectedness of AEs/event in this study will be the current IB.

8.1.1.4 Laboratory Test Abnormalities

All abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They result in a change in IIP schedule of administration (change in dosage, delay in administration, IIP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator, or the laboratory test abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline based on sponsor review.

8.1.1.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.1.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g., electrocardiogram changes) that result in a change in IIP dosage or administration schedule, or in discontinuation of the IIP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.2 Recording and Follow up of Adverse Events

At each visit, the subject should be asked a non-leading question such as: “How have you felt since the administration or last administration of the study compound.”

All observed or volunteered AEs, regardless of study arm or suspected causal relationship to IIP, will be recorded on the AE page(s) of the eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbations of pre-existing illnesses should be recorded according to NCI terminology.

Any AEs already recorded and designated as ‘continuing’ should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IIP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE, after the date of IIP discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

8.1.3 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of study arm or suspected relationship to IIP must be reported immediately (within 24 hours of the investigator's knowledge of the event) using the fax number specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE that:

1) Results in death,
2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,
3) Results in inpatient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),
4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,
5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IIP,
6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit.
- **Prolongation of hospitalisation** is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria

for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.

- Pre-planned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae that meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), to Ipsen Pharmacovigilance through the email (preferably) or fax number specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IIP administration occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor within 24 hours for each SAE:

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.4 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IIP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected after the study and it may be necessary to discontinue administration of the IIP.

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor as an SAE. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all subjects to inform them immediately should they or their female partner become pregnant during the study. In case the investigator becomes aware of pregnancy occurring in a subject (pregnancy test before each exposure to the IIP), the IIP administration should be stopped and the subject followed up until Visit 4 (End of the study). The investigator should counsel the subject, discuss the risks, if any, and the possible effects on the foetus. Monitoring of the subject (or female partner of a male subject) who becomes pregnant during the study after the administration of at least one of the two single IIP injections should continue until conclusion of the pregnancy, which may involve follow up after the subject's involvement in the study has ended (as per Ipsen's standard pharmacovigilance).

Pregnancies with a probable conception date within completion of the study (30 days after subject's last dose of IIP) must also be reported to the investigator for onward reporting to the sponsor.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, this should be reported to the sponsor. After the partner has given written consent, she should be counselled and followed as described above. Monitoring of the partner should continue until the pregnancy comes to an end.

8.1.5 Deaths

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 8.1.1.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these four AE options:

- Death not otherwise specified (NOS),
- Disease progression NOS,
- Multi-organ failure,
- Sudden death.

The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g. after autopsy), "unexplained death" should be replaced by the established cause of death."

8.1.6 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IIP (see Section 4.3).

If the second dose of IIP cannot be given due to a SAE following Visit 2 administration, it must be reported immediately to the sponsor's designated representative (see Section 8.1.3).

In all cases, the investigator must ensure the subject is adequately followed up (see Section 8.1.2).

Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the CA, independent ethics committees (IECs) and other investigators concerned by the IIP. Reporting will be done in accordance with the applicable regulatory requirements.

For study centres in the USA, Investigational New Drug (IND) application safety reports will be submitted directly to the investigators. It is the investigators' responsibility to notify their institutional review board (IRB) in a timely manner.

8.2 Clinical Laboratory Tests

Blood samples will be collected at all study visits (Screening Visit [Visit 1], Baseline/Day 1 [Visit 2], Visit 3, and End of Study/Early Withdrawal [Visit 4]) (see schedule of assessment in Table 5) or the evaluation of haematology and serum chemistry. Urine samples will be collected only at Visit 2 and Visit 3 to determine the amount of renal excretion of OPS202.

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant result occurring or observed during the study in the AE section of the eCRF (see Section 8.1.1.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to Baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Blood samples will be collected (in a potassium ethylenediaminetetraacetic acid [EDTA] tube) to assess the following parameters: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) absolute count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count.

8.2.2 Blood Biochemistry

Blood samples will be collected to assess the following parameters:

- urea, creatinine, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- AP, AST, ALT, gamma-glutamyl transferase (GGT)
- albumin, total protein, total cholesterol, triglycerides, fasting glucose

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocyte esterase, glucose and specific gravity by dipstick.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

8.2.4 Pregnancy Test

A ßHCG test will be performed for all female subjects of childbearing potential at Screening (Visit 1) and End of Study Visit (Visit 4). A urinary hCG test will be performed at Baseline Visit (Visit 2) before first IIP administration and at Visit 3 before second IIP administration and if clinically indicated. Any subject becoming pregnant during the study will be withdrawn. All pregnancies (including in female partners of male participants) that occur during the study are to be reported as described in Section 8.1.4.

8.2.5 Putative Antibody Testing

Not applicable

8.2.6 Other Clinical Laboratory Tests

Not applicable.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted at Screening, Baseline (Visit 2), Visit 3 and End of Study (Visit 4)/Early Withdrawal (see Table 5), and height will be measured at Screening.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes rest in sitting position and after one minute standing. Absolute values and change from Baseline will be analysed.

Respiratory rate and temperature (tympanic/oral) will be recorded.

8.5 Electrocardiography

An ECG analysis will be included as a safety evaluation/endpoint in this study.

The ECGs will be recorded at Screening Visit, and End of Study/Early Withdrawal (Visit 4).

Twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR, PR, QRS, QT) can be measured automatically as per study site usual practice. The ECG will be recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available. ECG interval estimates will be measured as per study site usual practice, in this study.

Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

9.1 Pharmacokinetics

9.1.1 Sample Collection

Subjects randomized to each of the six dose range combinations of peptide mass and radioactivity will participate in the OPS202 PK sampling.

Blood samples (2 mL each) for determination of OPS202 plasma concentrations will be collected preferably by venepuncture in low-binding tubes at the following timepoints: Baseline pre-dose (T0), 5 min, 15 to 45min, 1h, 2h, 3h and 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits (Visit 2 and Visit 3).

Urine collection in low-binding containers to determine renal excretion of OPS202 will be performed over the first 6 hours (0h to 3h and 3h to 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits: Visit 2 and Visit 3). Subjects will be asked to empty his/her bladder just before the ^{68}Ga-OPS202 i.v. administration and then all urine voided during the collection interval (0-6 hours post ^{68}Ga-OPS202 i.v. administration) will be collected and stored.

All details about sample collection, storage and shipment will be provided in the Pharmacokinetics, Dynamics and Metabolism (PDM) Sample Management Plan/Laboratory Manual.

During the study, the nominal sample collection times may be changed, but the total number of samples will not increase. The exact dates and times of blood sample collection and study drug administration must be recorded in the eCRF.

9.1.2 Analytical Procedures

Plasma samples will be analysed to determine concentrations of OPS202 using a validated, specific and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method at Kymos Pharma Services, Barcelona, Spain. As an exploratory analysis, some of the additional plasma samples may be used to measure potential metabolites (identified during pre-clinical investigations) using a qualified LC-MS/MS method.
Urine samples will be analysed to determine concentrations of OPS202 using a validated method. As an exploratory analysis, some of the urine samples might be used to explore potential metabolites.

9.1.3 Data Analysis

Individual plasma and urine concentrations for OPS202 will be listed and summarised by timepoints and dose range combinations using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation assuming log-normally distributed data). Linear and semilogarithmics plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

Analysis of plasma and urine PK data by non-compartmental approach using Phoenix WinNonLin Version 6.3 or higher will be documented in a separate analysis plan. The analysis of PK data will be performed by a CRO under Ipsen Clinical PK department's supervision and if warranted by the data the following parameters, but not limited to, will be computed:

- C_{max}
- AUC_{last}
- AUC_{∞}

- Elimination half-life ($T_{1/2}$)
- Total plasma clearance (CL)
- Volume of distribution (V)
- Excreted amount in the urine over each time interval (0h to 3h and 3h to 6h after the ^{68}Ga-OPS202 i.v. administration at the corresponding visits: Visit 2 and Visit 3), as well as the 6-hour Ae).

Descriptive summary statistics (the number of observations [n], mean, median, standard deviation [SD] and range for continuous variables, and n and per cent [%] for categorical/nominal variables) will be presented for each PK parameter.

Additional exploratory model-based analysis (population PK analysis) might also be conducted using NONMEM software.

10 STATISTICS

10.1 Analysis Populations

The following population definitions will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Randomised population**: All subjects randomly assigned to a dosing arm / sequence.
- **Safety population**: All subjects who received at least one dose of study medication
- **Per protocol (PP) population**: All randomised subjects for whom no major protocol deviations occurred.
- **Pharmacokinetics population**: All randomised subjects who received at least one dose of ^{68}Ga-OPS202 and have no major protocol deviations affecting the PK variables and who have a sufficient number of plasma concentrations to estimate the main PK parameters (C_{max}, AUC_{last}, etc.) and at least one PK sample analysed.

10.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint will be performed on the PP population. In addition, secondary/confirmatory analysis may be performed on randomised population.

The analyses of safety data will be performed based on the safety population.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 12.1.2 for definition) will be described in the Protocol Deviation Document and its impact on inclusion in each analysis population (randomised, PP and safety populations) for any subject will be specified. The final list of protocol deviations impacting the safety, randomised and PP populations will be reviewed prior to database lock, before any unblinding of central reads. The list may be updated up to the database lock to include any additional major protocol deviations impacting inclusion in the PP population.

The list of major protocol deviations impacting inclusion in the PP population will be reviewed during the data review meeting held prior to database lock and before the unblinding central reads. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population. Of note, if the screening visit duration is extended due to confirmation by ICL of eligibility regarding somatostatin receptor scan, this will not be considered a protocol deviation.

10.2 Sample Size Determination

It is anticipated that a total of 24 evaluable subjects will complete the study (i.e., receive 2 of the six combinations of dose ranges offered per protocol) and therefore to account for illegible or missing scans subjects with unacceptable scan images will be replaced, in order to obtain at least 8 evaluable subjects in each study arm. This is considered appropriate for a descriptive analysis and it is not based on formal statistical sample size calculation.

To limit the extension of study duration if the last two potentially evaluable subjects (randomisation numbers CCI) should be non-evaluable, corresponding replacement subjects (randomisation number CCI , respectively) will be recruited as soon as possible. If both potentially evaluable and replacement subjects are evaluable at the end of the study, the subjects assigned to randomisation numbers CCI will be included in the efficacy and safety analysis whereas the replacement subjects assigned to

randomisation numbers [redacted] will be included only in the safety analysis. Therefore, a total of at least 25 subjects will be enrolled in the study to ensure the 48 PET scans for the analysis.

10.3 Significance Testing and Estimations

The analysis will be descriptive and no formal statistical tests are planned for the primary and secondary endpoints.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A Reporting and Analysis Plan describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 8 or higher).

10.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, SD, median, minimum, maximum) and frequency counts of demographic and baseline data (medical history, concomitant disease, predosing AEs and ongoing medical history, prior medications and therapies, baseline symptoms, etc.) will be presented by study arm and overall for the randomised and PP populations.

10.4.2 Homogeneity of Treatment Groups

Not applicable.

10.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the randomised, PP and safety populations will be tabulated by arm. The reasons for subject exclusions from each of the populations will be listed and tabulated by arm. In addition, the numbers of subjects who were randomised, received IIP, discontinued and completed at each of the study periods (e.g. Visit 2 and Visit 3, active follow-up period) will be tabulated by arm. Primary reasons for discontinuation of study IIP will be listed and tabulated by arm.

10.4.4 Pharmacokinetic Data

The pharmacokinetic data analysis will be performed independently by a CRO under Ipsen Clinical PK department's supervision as described in Section 9.1.3.

Individual listings and summary tables of OPS202 plasma concentrations and amount excreted in urine will be provided.

10.4.5 Efficacy Evaluation

As indicated in Section 7.1, the primary efficacy variable is the differences in relative lesion counts derived from a 2 × 3 factorial analysis measuring the ratio of the number of lesions detected by ^{68}Ga-OPS202 to the number of lesions assessed by standard-of-truth, for each combination of injected peptide/radioactivity dose ranges. Primary efficacy variable will be summarised by study arm and by each combination peptide/radioactivity dose range.

As indicated in Section 7.2, the secondary efficacy variables are the below listed variables measured at Visit 2 and Visit 3 after the i.v. administration of the IIP:

Key Secondary Endpoint:

- Differences in image quality derived from a 2 × 3 factorial analysis measuring, for each combination of injected peptide/radioactivity dose ranges, the tumour-to-background ratio in each of the major anatomic sites (descriptive analyses for liver, lymph nodes, bone and lungs). Key secondary efficacy variable will be summarised by study arm and by each combination peptide/radioactivity dose range. A qualitative analysis of the image assessed by the blinded readers will be performed to back up the quantitative quality measured by tumour-to-background analysis.

Other Secondary Endpoints:

- Differences of lesion SUV_{max} between the two peptide mass dose ranges and the three radioactivity dose ranges measured in the most avid lesions (descriptive analyses for up to a maximum of five lesions per organ), in liver, lymph nodes, bone and lungs
- Differences of absolute number of lesions between the two peptide mass dose ranges and the three radioactivity dose ranges detected in each of the following anatomic sites:
  - Primary site of GEP-NET
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs.

Exploratory Endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to standard-of-truth
- Comparison to sstr2 agonist positive scan results will be computed for sensitivity analysis
- Differences in SUV_{max} ratios between the two peptide mass dose ranges and three radioactivity dose ranges for lesions
- SNR calculated from lesion-free VOI in the liver: SUV_{mean}/SUV_{SD} between the three radioactivity doses.

10.4.6 Adjustment for Country/Centre Effect

It is not planned to perform a subgroup analysis on centres.

10.4.7 Safety Evaluation

All AEs will be coded according to the MedDRA version (latest version in use) and will be classified by MedDRA SOC and PT. AEs, SAEs, AEs leading to discontinuation of study treatment, and AEs leading to death will be summarized and listed by subject, SOC class and PT. Adverse events reported by investigators using the NCI-CTCAE classification (version 5.0) will be coded using MedDRA dictionary (latest available version).

Incidence of all reported AEs and SAEs will be tabulated by dosing arm and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs associated with premature withdrawal of study medication.

Concomitant medication will be coded by using WHO Drug Dictionary (WHO-DD) (latest available version) and will be summarised by dosing arm and by overall.

Summary statistics (mean, median, SD and range as appropriate) by IIP dose ranges combination and overall will be presented for vital signs, blood pressure, heart rate, ECG parameters, clinical laboratory tests etc. at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically

significant abnormal values will be presented. Clinically significant ECG findings will also be flagged. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

Summary incidence tables will be provided classified by SOC, PT, and associated NCI-CTCAE worst grade. In the event of multiple occurrences of the same AEs being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) will be chosen.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTCAE criteria. The NCI-CTCAE grade 3 and 4 haematology and biochemistry parameters by subject and by cycle will be listed.

10.5 Subgroup Analyses

Not applicable.

10.6 Interim Analyses

An interim analysis will be performed when a minimum of 12 subjects have fully completed the study. The study will continue while the interim analysis is performed and the study may be stopped per sponsor's decision based on expert review of the data. The interim statistical analysis plan will provide further details of the statistical analyses.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 12.4, and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations, Violations, and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative (see Section 10.1).

A major protocol deviation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

Generally, a protocol deviation qualifies as major if:

- The deviation has harmed or posed a significant or substantive risk of harm to the research subject
- The deviation compromises the scientific integrity of the data collected for the study
- The deviation is a willful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)
- The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures
- The deviation is inconsistent with Ipsen's research, medical and ethical principles.

See also Section 10.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

A minor protocol deviation is any significant divergence from the protocol that does not impact the study results.

12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved, or new information becomes available). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory printouts) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.1), and FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

13.2 Informed Consent

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IIP). Sufficient time will be allowed to discuss any questions raised by the subject.

The sponsor will provide a sample informed consent form. The final version-controlled form must be agreed to by the sponsor, and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.

The consent form may need to be revised during the study following a protocol amendment that includes important new information relevant to the safety of the subject. In this instance approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, IIP administration, laboratory data, safety data on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

14.2 Data Management

An EDC system will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the contracted CRO standard operating procedures (SOPs), unless otherwise specified. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Monitoring Procedures). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of AEs, medical history, concomitant medication, procedure and non-drug therapy terms will be performed centrally by the specialised CRO, directed by the sponsor's Biometry Group, and reviewed and approved by the sponsor. Concomitant medications will be coded

using WHO-DD (latest available version) and AEs/medical history terms will be coded using MedDRA (latest available version).

14.3 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

15 FINANCING AND INSURANCE

15.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol, and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by FDA 21 CFR Part 54.

15.2 Insurance, Indemnity and Compensation

The sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital-specific indemnity agreement will be used.

16 REPORTING AND PUBLICATIONS OF RESULTS

16.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at this stage of the study.

16.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

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