STATISTICAL AND ANALYSIS PLAN

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)

PROTOCOL VERSION AND DATE: 5.0 – 02 MAY 2019
VERSION 5.1 AMENDEMENT 3.1 (DENMARK): 02 MAY 2019

SAP Version	Date
Final Version 1.0	10 August 2017
Final Version 2.0	03 July 2019
Final Version 3.0	28 October 2019

STUDY NUMBER:	D-FR-01070-002
EUDRACT NUMBER	2016 004928 39
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)
SAP VERSION:	Final Version 3.0
SAP DATE:	28 October 2019

Further to your review and agreement to the Statistical and Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Clinical Statistics Manager or designee	PPD PPD Ipsen Bioscience, Cambridge, Massachusetts, U.S.		
Medical Development Director	PPD Ipsen Pharma 65 quai Georges Gorse 92100 Boulogne-Billancourt France		

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study statistician	PPD PPD PPD SARL		
Manager statistician	PPD PPD PPD SARL		

IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical and Analysis Plan version became the Final Statistical and Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
		10 August 2017	03 July 2019	Major changes: • Reference to Protocol Version 5.0 and 5.1 • Update for sponsor and CRO team members (name of approvers, CRO name from Chiltern to Covance) • Section 2.1.2: Definition for PP population is clarified for subjects having PET/CT scan non evaluable by ICL • Section 3.2.1.1: Update of SOT definition based on both time points together (instead of maximal), and addition of analysis of adjudication rate and two additional listings • Section 3.2.1.2 a): Update formula for tumour-to-background ratio, and specification of background location in listings. Quality score: Analysis of sum of both readers • Section 3.2.1.2 d) Update numerator of formula • Section 3.2.1.2 e) and f) Update of exploratory efficacy endpoints • Section 3.2.1.2 g) Update formula for SUV_{max} ratio • Section 3.2.2 Removal of some analyses no longer required • Section 3.2.16 completed with description of planned interim analysis, according to Protocol Version 5.0. • Section 5 updated

		03 July 2019	28 October 2019	Major changes: • Removal of radioactivity dose by decay of time (that had been added in SAP V2.0) • Addition of a listing of SUV measurements per lesion • Update MBq/kg ranges to have balanced ranges • Addition of lab shift tables

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- **AE:** Adverse Event
- **ALP:** Alkaline phosphatase
- **ALT:** Alanine aminotransferase
- **AP:** Alkaline phosphatase
- **AST:** Aspartate aminotransferase
- **ATC:** Anatomical Therapeutic Chemical
- **AUC:** Area under the concentration time curve
- **$AUC_{0-\infty}$:** Area under the concentration time curve from time 0 to infinity
- **AUC_{last}:** Area under the concentration time curve from time 0 to the time of the last quantifiable concentration
- **BMI:** Body mass index
- **CA:** Competent Authorities
- **CL:** Total plasma clearance
- **C_{max}:** Maximum observed drug concentration
- **CRO:** Contract research organisation
- **CT:** Computed tomography
- **D:** Day
- **DICOM:** Digital Imaging and Communications in Medicine
- **e:** Electronic
- **ECG:** Electrocardiogram
- **ECOG:** Eastern Cooperative Oncology Group
- **eCRF:** Electronic case report form
- **EDC:** Electronic data capture
- **EOS:** End Of Study
- **EW:** Early Withdrawal
- **FN:** False Negative
- **FP:** False Positive
- **^{68}Ga:** Gallium - 68
- **GCP:** Good Clinical Practice
- **GEP-NET:** Gastroenteropancreatic Neuroendocrine Tumour
- **GGT:** Gamma-Glutamyl Transferase

- **GMP:** Good Manufacturing Practice
- **HCG:** Human chorionic gonadotropin
- **i.v.:** Intravenous
- **ICH:** International Conference on Harmonisation
- **ICL:** Imaging core lab
- **IEC:** Independent ethics committee
- **IIP:** Investigational Imaging Product
- **IRB:** Institutional review board
- **IRC:** Imaging review charter
- **LLN:** Lower limit of normal range
- **max:** Maximum
- **MBq:** Megabecquerel
- **MCH:** Mean corpuscular haemoglobin
- **MCHC:** Mean corpuscular haemoglobin concentration
- **MCV:** Mean corpuscular volume
- **MedDRA:** Medical Dictionary for Regulatory Activities
- **min:** Minimum
- **NCI-CTCAE:** National Cancer Institute - Common Terminology Criteria for Adverse Events
- **NEC:** Neuroendocrine carcinoma
- **PD:** Pharmacodynamics
- **PDD:** Protocol Deviations Document
- **PDM:** Pharmacokinetics & Drug Metabolism
- **PET:** Positron emission tomography
- **PK:** Pharmacokinetics
- **PP:** Per Protocol
- **PT:** Preferred Term
- **QC:** Quality control
- **QRS:** QRS interval duration
- **QT:** Time interval for ventricular depolarisation and repolarisation
- **QTc:** Corrected QT interval
- **RBC:** Red blood cell

- **SAE:** Serious Adverse Event
- **SAP:** Statistical and Analysis Plan
- **SAS®:** Statistical Analysis System®
- **SD:** Standard deviation
- **SI:** Standard International
- **SNR:** Signal-to-noise ratio
- **SOC:** System organ class
- **SOP:** Standard Operating Procedure
- **SOT:** Standard-of-truth
- **SSA:** Somatostatin analogues
- **sstr:** Somatostatin receptors
- **SUSAR:** Suspected unexpected serious adverse reaction
- **SUV:** Standardised uptake value
- **SUV_{max}:** maximum standardized uptake value
- **T½:** Elimination half life
- **TEAE:** Treatment Emergent Adverse Event
- **TFLs:** Tables, Figures and Listings
- **TN:** True Negative
- **TNM:** Tumour, node and metastasis
- **TP:** True Positive
- **ULN:** Upper limit of normal range
- **V:** Volume of distribution
- **VOI:** Volume of interest
- **WBC:** White blood cell
- **WHO:** World Health Organization
- **WHO-DD:** World Health Organization (WHO) Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

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 somatostatin receptor 2 (sstr2) positive gastroenteropancreatic neuroendocrine tumour (GEP-NET).

1.1.2 Secondary objectives

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.

1.1.3 Exploratory objectives

The exploratory objectives of the study include the following:

- 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 and signal-to-noise ratios (SNR).

1.2 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.

Table 1 Combinations of studied peptide mass dose ranges and radioactivity dose ranges

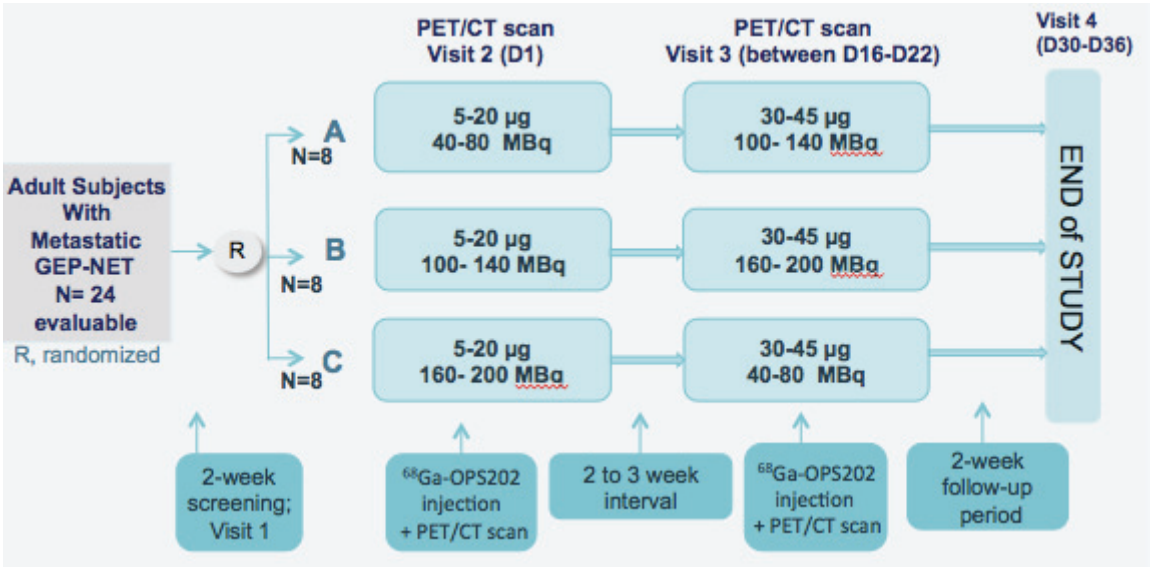
Peptide mass dose range	Radioactivity dose range		
	40-80 MBq	100-140 MBq	160-200 MBq
5 – 20 µg	8 scans	8 scans	8 scans
30 – 45 µg	8 scans	8 scans	8 scans

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)

Subjects will be assigned to one of three study arms (see Figure 1). 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 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.

Figure 1 Study Design and Subject Allocation



1.2.1 Study population

It is planned to enrol at least 25 subjects in 6 centres in the United States and Europe to ensure 24 evaluable subjects to complete the study.

Adults subjects with well-differentiated functioning or non-functioning metastatic GEP-NET (Grade I and II as per World Health Organization (WHO) classification 2010), and having positive sstr2 scan will be recruited in this study.

1.2.2 Study exposure

Recruitment is expected to last between 4 and 5 months.

Subject participation in the study is estimated to last approximately 6-7 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), after a 15- to 21-day time interval from the first administration (Visit 1)
- Visit 4: A 2-week follow-up period for evaluation of safety.

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 (EOS)/Early Withdrawal (EW) Visit (Visit 4).

Subjects who withdraw from the study before the completion of the second PET/CT scan evaluation will have Visit 4 (EOS/EW Visit [Visit 4]) or early termination procedures and assessments performed at their final visit. In case subject is lost to follow-up, date of termination will be specified, and an EW visit will be performed if possible. An EOS/EW Visit (Visit 4) will take place 2 weeks after the second PET/CT scan.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study.

A randomisation list will be prepared under the responsibility of the sponsor's biostatistics department.

After eligibility is confirmed at Visit 2 (Day 1), subjects will be assigned to a randomisation number and randomised to the associated sequence of the assigned 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.

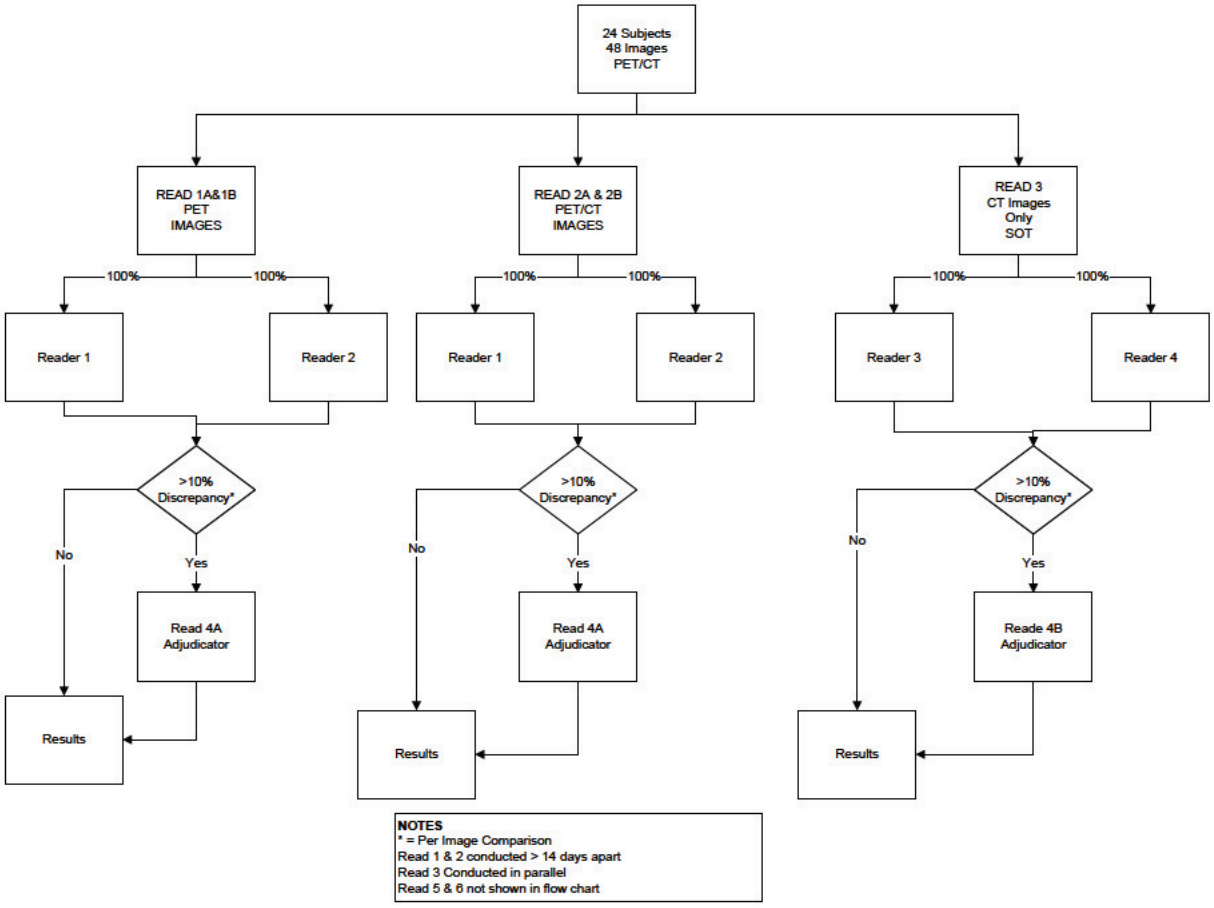
1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

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 if required. The readers will be specifically trained for this protocol.

All the images will be reviewed according to the workflow illustrated in the Figure 2 below.

Figure 2 Flow Chart of the Independent Review Methodology



Full details of the read design and conduct is provided in the Independent Review Charter (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. The independent readers will be blinded to subject, site, peptide mass dose, radioactivity dose, and the temporal sequence of dosing. 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 1) as a 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.

Details for computation and analysis of primary efficacy criterion are provided in section 3.2.1.1.

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 (SOT) 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) SUVmax 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 sstr2 receptor agonist positive scans.

1.3.2.2 Safety assessments

- Adverse Events

Adverse events (AEs) will be monitored from the time that the subject gives informed consent and throughout the study. AEs will be elicited by direct, nonleading questioning or by spontaneous reports.

AEs will be recorded and graded according to the current version of the National Cancer Institute Common Terminology Criteria for AEs (version 4.03, Dated 14 June 2010).

- Vital signs

Vital signs will be collected at each visit.

Blood pressure (systolic and diastolic) and heart rate will be assessed with an automated device so that measurements are independent of the observer. These parameters will be recorded after five minutes rest in sitting position and after one minute standing.

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

Any clinically significant abnormalities will be recorded as AEs.

- Physical Examination

Physical examination of major body systems, including body weight and height (screening only) will be conducted at each visit.

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.

- Electrocardiography

Electrocardiograms (ECGs) will be recorded at Screening Visit and EOS/EW (Visit 4).

Twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR interval, PR interval, QRS interval, QT and QTc) 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.

- Clinical Laboratory Tests

Blood samples will be collected at all study visits for the evaluation of haematology and serum chemistry.

Urine samples will be collected at all study visits for dipstick urinalysis.

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.

Haematology – the following parameters will be assessed: 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.

Blood Biochemistry – the following parameters will be assessed: urea, creatinine, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose

Urinalysis – the following parameters will be assessed: 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.

1.3.2.3 Other assessments

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

- Demographic data (date of birth/age, sex and race/ethnicity will be collected according to individual country regulations/requirements).
- Medical and surgical history, including ongoing conditions
- Prior and concomitant medications/therapies
- Prior and concomitant non-drug therapies
- Concomitant surgical procedures
- Collection of previous somatostatin receptor scan.
- Beta human chorionic gonadotropin (ß-HCG) pregnancy test for women of childbearing potential

Pharmacokinetic (PK) analyses - OPS202 blood and urine PK sampling will be performed for all subjects participating in the study.

PK analyses will be described in a separate Analysis Plan.

1.3.2.4 Withdrawal/discontinuation

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 of the protocol, noncompliance with the protocol conditions or AE).

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 EOS/EW Visit (Visit 4). Subjects who withdraw from the study before the completion of the second PET/CT scan evaluation will have Visit 4 (EOS/EW Visit [Visit 4]) or early termination procedures and assessments performed at their final visit. In case subject is lost to follow-up, date of termination will be specified, and the EW visit will be performed if possible.

An EOS/EW Visit (Visit 4) will take place 2 weeks after the second PET/CT scan.

1.3.3 Schedule of assessments

The schedule of procedures and assessments during the study is summarised in Table 2.

Table 2 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 Scan**: Results available in the preceding 6 months to screening (Visit 1). 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.

1.3.4 Planned sample size

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 (randomisation numbers CCI) should be non-evaluable, corresponding replacement subjects (randomisation number CCI , 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/CT 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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

The following populations will be used during statistical analyses:

- The ***screened population*****,** including all subjects screened (i.e., who signed the informed consent),
- The randomised population, including all subjects randomly assigned to a dosing arm / sequence,
- The Per Protocol (PP) population, including all randomised subjects for whom no major protocol violations/deviations impacting primary endpoint results occurred,
- The safety population, including all subjects who received at least one dose of investigational imaging product (IIP),
- The pharmacokinetics (PK) population, including all subjects assessable for PK.

For each population of analysis, further description and specificities are provided below.

To describe the study populations, a summary table with number of subjects enrolled into each population will be provided by randomisation arm.

2.1 Efficacy populations

2.1.1 Randomised population

The randomised population includes all subjects randomly assigned to a dosing arm / sequence.

Of note, replacement subjects will be included in randomised population.

2.1.2 Per Protocol population (PP)

The Per Protocol (PP) population includes all randomised subjects for whom no major protocol violations/deviations impacting primary endpoint results occurred.

Any subject having a PET/CT scan which is non-evaluable/non-readable or having not meet the required minimum number of lesions by ICL readers and/or adjudicator will be considered impacting primary endpoint results, and therefore will be excluded from PP population. If there are disagreements between the readers, the adjudicator will have the final verdict if scans are evaluable or readable and how many number of lesions are seen.

Criteria for exclusion from the PP population will be provided in a separate Protocol Deviations Document (PDD) and Protocol Deviations Specifications.

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.

The Per Protocol criteria should be produced in advance of the database lock and generation of the PP population, and should be done using the first 50% of the subjects to avoid potential bias. In addition, a more extensive list of protocol deviations may be defined and reported in data listings.

Data will be excluded from the PP population on a subject basis and not on a visit basis. Of note, in case a subject performs only one of the two planned injections, he will be excluded from the PP population.

Reasons for subject exclusion from PP population will be presented in a summary table by dosing arm / sequence.

As specified in the study protocol section 3.3, replacement subjects of subjects CCI will be recruited as soon as possible. In case subjects CCI are found to be evaluable, corresponding replacement subjects will be excluded from PP population, regardless of the presence of major of protocol deviations (and provided CCI have actually been replaced). Of note, correspondence between replacement subjects and their original subject will be obtained using the listing of randomised subjects from Medidata Balance (eCRF module for randomisation). This listing will be imported at the time of programming the statistical analysis.

As a results, PP population is expected to include 24 subjects: 8 subjects in each of the three study arms, who did not present with any major protocol deviation impacting PP and who were not replaced for any reason.

2.2 Safety population

The safety population includes all subjects who received at least one dose of investigational imaging product (IIP).

In case a subject received IIP but did not sign the informed consent, he will be included into safety population.

The safety population will be analysed using subjects as treated.

2.3 Pharmacokinetics

2.3.1 Pharmacokinetics (PK) population

The PK population includes all randomised subjects who received at least one dose of ^{68}Ga-OPS202 and who have no major protocol deviations affecting the PK variables and who have a sufficient number of plasma concentrations to estimate the main PK parameters (maximum observed drug concentration (C_{max}), area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}), etc.) and have at least one PK sample analysed.

2.4 Primary population

The primary efficacy analysis will be performed on the PP population. A supportive post-hoc analysis of primary efficacy criterion may be performed on randomised population, considering all scans assessments available in ICL database, in case the number of available assessments for non-PP subjects is considered sufficient.

All secondary and exploratory efficacy endpoints will be evaluated on the PP population.

The assessment of safety and tolerability will be based on the safety population.

The PK analysis will be based on the PK population.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with International Conference on Harmonisation (ICH) E9 guideline [1] and will be based on the pooled data from the individual study sites, unless otherwise stated.

When overall statistics are provided in addition to the statistics by study arm/dosing combination, it is for descriptive purpose only and not for inferential purpose to any population.

Statistical analyses of efficacy and safety criteria will be performed by Chiltern International.

The analysis of plasma and urine PK data will be performed by PPD), a clinical research organisation (CRO) under Ipsen Pharmacokinetics & Drug Metabolism (PDM) department's supervision.

3.1.1 Primary efficacy endpoint(s)

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 SOT (descriptive analyses).

The SOT in this study is the CT scan images acquired at Visit 2 and Visit 3.

3.1.2 Secondary efficacy endpoint(s)

Key Secondary Endpoint:

(a) 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 (i.e., 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:

(b) Differences in lesion SUVmax 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)

(c) 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 (bones)
- Lungs

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

Exploratory Endpoints:

(e) Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to SOT

(f) Comparison to sstr2 agonist positive scan results will be computed for sensitivity analysis

(g) Differences in SUVmax ratios between the two peptide mass dose ranges and three radioactivity dose ranges for lesions

(h) SNR calculated from lesion-free volume of interest (VOI) in the liver: SUVmean/SUVSD between the three radioactivity doses

3.1.3 Safety endpoint(s)

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), 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 - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, 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 4.03). 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.

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

The statistical analysis of efficacy and safety is descriptive, therefore no formal statistical significance testing will be performed.

3.2 Analysis methods

3.2.1 Efficacy

All efficacy analyses will be based on the centralised review of scans imaging performed under the responsibility of the ICL.

As specified in the description of each efficacy criterion thereafter:

- Analysis will be based on PET/CT and/or PET alone assessments,
- SOT will be defined as CT alone or sstr2 agonist positive scan, as specified below.

Scan acquisition times (refer to Appendix 1, Derived data) will be listed by subject and visit and will be summarised for each of the six combinations of injected peptide/radioactivity dose range.

3.2.1.1 Primary efficacy analysis

The primary endpoint is the relative lesion count, measuring the ratio of the number of lesions detected by ^{68}Ga-OPS202 to the number of lesions assessed by SOT.

The SOT is the CT scan images acquired at Visit 2 and Visit 3, using number of lesions identified by the reader on both timepoints together (provided by ICL), in order to take into account potential variability within subject or partial volume effect.

For each PET/CT assessment, this ratio will be computed, as indicated below:

$$Relative\ lesion\ count\ = \frac{Number\ of\ lesions\ detected\ by\ 68Ga-OPS202}{Number\ of\ lesions\ detected\ by\ SOT}$$

Numerator and denominator will be available in the database provided by ICL.

Selection of the optimal dose range for peptide mass and radioactivity of ^{68}Ga-OPS202 will be based on the observed highest relative lesion counts, based on provided descriptive statistics: n (number of non-missing observations), number of missing values (if any), arithmetic mean, standard deviation (SD), median and the range (minimum, maximum). Those descriptive statistics will be used for analysing all continuous parameters.

Analysis over all organs

For each PET/CT and PET assessment, relative lesion count will be computed over all lesions of all organs.

The denominator, based on SOT, will be computed over all organs.

Analysis per organ

For each PET/CT and PET assessment, relative lesion count will be computed for each of the following organs:

- Primary site of GEP-NET (among all subjects with at least one lesion detected by SOT on primary site of GEP-NET).
- Lymph nodes (among all subjects with at least one lesion detected by SOT on lymph nodes).
- Liver (among all assessed subjects with at least one lesion detected by SOT on liver).

- Axial/appendicular skeleton (bones) (among all assessed subjects with at least one lesion detected by SOT in bones).
- Lungs (among all assessed subjects with at least one lesion detected by SOT in lungs).

The denominator, based on SOT, will be computed for each organ.

Relative lesion count (over all organs then per organ) will be summarised using descriptive statistics for:

- each of the six combinations of injected peptide/radioactivity dose range, presented in such a way that study arms are explicit
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

No statistical test will be performed (no p-value nor confidence interval).

Following SAS code will be used:

```
PROC UNIVARIATE DATA=dset NOPRINT;
        VAR var1;
        BY arm;
        OUTPUT OUT=outname
        N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std Q1=q1
Q3=q3;
RUN;
```

Figures will also be provided for describing primary efficacy criteria over all organs:

- One box-plot for each of the six combinations. Box plot should indicate mean (symbol), median (line into the box), Q1 (bottom of box), Q3 (top of box), and minimum and maximum should be extremities of lines outside the box.
- One bar chart of individual values per combination (in theory 8 subjects within each combination, so a total of 48 bars)

For the per organ analysis, a similar set of figures will be provided, if at least 4 subjects have lesions detected by SOT in this organ.

Primary analysis will be performed on PP population.

A supportive post-hoc analysis of primary efficacy criterion (over all organs and per organ) may be performed on randomised population, considering all scans assessments available in ICL database, in case the number of available assessments for non-PP subjects is considered sufficient.

Individual values of number of lesions detected by ^{68}Ga-OPS202, number of lesions detected by SOT (CT scan), and relative lesion count will be listed by randomisation arm, by subject and by visit for both types of assessment (PET/CT and PET).

In addition, the adjudication rates, defined as the number of reads which goes to adjudication over the total number of reads, will be computed per organ for each of the six combinations of injected peptide/radioactivity dose range and overall.

Two additional listings will also be presented:
- listing of all discrepancies between both readers,
- listing of subjects with multiple (two or more) adjudications.

Both listings will be sorted by subject, organ and visit.

3.2.1.2 Secondary efficacy analysis

All secondary and exploratory analyses will be performed on PP population only.

Selection of the optimal dose range for peptide mass and radioactivity of ^{68}Ga-OPS202 will be based on the provided descriptive statistics for all secondary and exploratory efficacy endpoints, in addition to primary endpoint.

Key Secondary Endpoint:

a) Image quality

Quantitative measure:

For each PET assessment, image quality will be quantitatively measured by the tumour-to-background ratio, which will be obtained using the mean of all lesions tumour-to-backgrounds, for each of the four following organs:

- Liver
- Lymph nodes
- Bone
- Lungs

For up to five most avid lesions per organ that are confirmed by SOT, the tumour-to-background ratio will be computed as lesion SUV_{mean} divided by the SUV_{mean} of the subject's reference tissue (tumour-free liver or aortic blood).

Tumour-to-background ratio is a unit-less measure. A high tumour-to-background ratio indicates high effectiveness of ^{68}Ga-OPS202 as a diagnostic agent.

Tumour-to-background ratio will be analysed using descriptive statistics, presented for each of the four organs and for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

Individual values of tumour-to-background ratio will be listed by subject, by organ and by visit.

Background location will be specified (L: Liver, B = Aortic blood).

Qualitative measure:

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. This qualitative assessment will be performed using a quality score.

For each PET/CT and PET assessment, each independent blinded reader will perform a direct comparison of the two ^{68}Ga-OPS202 scans (Visit 2 and Visit 3, that have with different peptide and radioactivity doses). He/she will note which of the pair provides superior images based on overall image quality and lesion count, attributing a score for each assessment.

The score for the assessment having superior images will be set to "1", and score for the assessment not selected will be set to "0". In case of equal quality, both assessments will have a score of "1".

Values will be available in the database provided by ICL.

Quality score will be analysed using descriptive statistics (frequencies and percentage), presented for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

Two sets of analysis will be performed for quality score:

- Based on assessment by reader A
- Based on assessment by reader B

Besides, readers scores will also be summed up together and presented for each of the six combinations of injected peptide/radioactivity dose range.

Individual values of quality score as well as which scan do reader prefer and reason for selecting scan 2 or 3 will be listed per reader, then by subject and by visit for both types of assessment (PET/CT and PET).

Other Secondary Endpoints:

b) Lesion SUV_{max}

For each PET assessment, lesion SUV_{max} (unit-less measure) will be measured for each lesion, up to a maximum of five most avid lesions per organ that are confirmed by SOT. In order to obtain a unique measure per organ, mean of the SUV_{max} will be computed within each of the four following organs:

- Liver
- Lymph nodes
- Bone
- Lungs.

Values will be available in the database provided by ICL.

Lesion SUV_{max} will be analysed using descriptive statistics, presented per organ and for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges.

Individual values will be listed by subject, by organ and by visit.

c) Absolute number of lesions detected by ^{68}Ga-OPS202, both as standalone and also compared to SOT

For each PET/CT and PET assessment, the number of lesions detected by ^{68}Ga-OPS202 and by SOT will be reported for each of the five following anatomic sites:

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

Values will be available in the database provided by ICL.

Absolute number of lesions detected by ^{68}Ga-OPS202 and difference with number of lesions detected by SOT will be analysed using descriptive statistics (for continuous variable), presented per anatomic site and for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

Also, for comparing lesions detection between 68Ga-OPS202 and SOT, the following analyses will be performed:

- Number of subjects having lesions detected by ^{68}Ga-OPS202 when no lesions is detected by SOT (so called “False Positive” lesions, although in this instance, without histology, this determination is equivocal), in each of five anatomic sites (Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs).
- Number of subjects having lesions detected by SOT when no lesions is detected by ^{68}Ga-OPS202 (so called “False negative” lesions, although in this instance, without histology, this determination is equivocal), in each of five anatomic sites (Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs).

Individual values of number of lesions detected by ^{68}Ga-OPS202 and difference with number of lesions detected by SOT will be listed by subject, by anatomic site and by visit for both types of assessment (PET/CT and PET),

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

For each subject's visit, the radioactivity dose/kg (in MBq/kg) will be computed using following formula:

$$Radioactivity\ dose/kg\ = \frac{Injected\ radioactivity\ dose\ at\ visit\ \ (MBq)}{Patient's\ weight\ at\ visit\ (kg)\ *}$$

*In case subject's weight is not available at visit, last weight value will be used.

First, as a preliminary step, a boxplot will be drawn in order to describe subjects' weight at Visit 2, for each of 6 combinations of injected peptide/radioactivity dose range.

The following efficacy criteria will be analysed:

- Primary criterion: Relative lesion count (overall and per each of the five anatomic sites)
- Secondary criteria: Image quality (tumour-to-background ratio for each of the four organs, quality score), lesion SUV_{max} in each of the four organs, absolute number of lesions in each of the five anatomic sites, difference between number of lesions detected by ^{68}Ga-OPS202 and number of lesions detected by SOT.

As graphical analysis of the radioactivity dose/kg, the following plots will be performed (plot of individual values) with both peptide dose ranges shown by using two different symbols:

- Scatterplot of radioactivity dose/kg x relative lesion count, per organ and overall
- Scatterplot of radioactivity dose/kg x tumour-to-background ratio, for each of the four organs (Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs)
- Scatterplot of radioactivity dose/kg x quality score
- Scatterplot of radioactivity dose/kg x SUV_{max}, per each of the four organs
- Scatterplot of radioactivity dose/kg x absolute number of lesions detected by ^{68}Ga-OPS202, per each of the five anatomic sites (Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs).
- Scatterplot of radioactivity dose/kg x difference between number of lesions detected by ^{68}Ga-OPS202 and number of lesion detected by SOT, per each of the five anatomic sites.

Besides, as categorical analysis of the radioactivity dose/kg, the following ranges will be used for the analysis, based on the observed distribution of the continuous radioactivity dose/kg among PP population:

- [min-Q1] MBq/kg
-]Q1-median] MBq/kg
-]median-Q3] MBq/kg
-]Q3-max] MBq/kg

Based on those ranges, summary tables with descriptive statistics for each of the four ranges of radioactivity dose/kg will be provided. Also, into each of the four ranges of radioactivity dose/kg, the two peptide doses will be analysed, that will lead to analyse, with same methodology as previously, 8 combinations of radioactivity dose/kg x peptide mass dose ranges.

Listings of individual values will be provided by ascending radioactivity dose/kg range then by ascending radioactivity dose/kg, and by subject (and by organ when applicable).

Exploratory efficacy endpoints:

e) Preliminary diagnostic sensitivity of 68Ga-OPS202 imaging of GEP-NETs by both subject-based and lesion-based analysis compared to standard-of-truth; and organ-based specificity, by radioactivity dose range (i.e. 40-80 MBq, 100-140 MBq, 160-200 MBq, 100-200 MBq, 40-200 MBq).

Diagnostic sensitivity between 68Ga-OPS202 and SOT will be assessed using performance specified in table below.

Table 3 Diagnostic performance of ^{68}Ga-OPS202 compared to SOT

^{68}Ga-OPS202 PET/CT scan results	**SOT results**	
	# of lesions detected	**# of lesions not detected**
# of lesions detected	True Positive (TP)	False Positive (FP)
# of lesions not detected	False Negative (FN)	True Negative (TN)

The sensitivity corresponds to the probability that the ^{68}Ga-OPS202 imaging detects the lesions, given that the lesions are positive in SOT.

For each PET/CT assessment, the sensitivity will be computed using following formula, per each of the organs (lesion-based approach) and overall (subject-based approach):

$$Sensitivity = \frac{TP}{TP + FN}$$

For lesion-based approach (per organ), following organs will be analysed: Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton, Lungs. In case no lesions were detected by the SOT, sensitivity cannot be computed due to null denominator. Therefore only organs with lesions detected by SoT will be analysed for sensitivity.

To allow for computation of sensitivity, detected lesions will be counted from the "Lesion Matching Table" provided by ICL.

Additionally, an organ-based specificity analysis will be performed, based on PET/CT assessments.

For each organ:

- If there are 0 lesions detected in an organ on both ^{68}Ga-OPS202 scan and SOT, it will be counted as TN.
- If there is at least 1 lesion detected in an organ on ^{68}Ga-OPS202 scan but not on SOT, it will be counted as FP.

Example for a given subject, a given visit VX:

	At least one lesion detected by ^{68}Ga-OPS202 at Visit VX	**At least one lesion detected by SOT**	**Type of lesion for analysis**
Primary site of GEP-NET	No	Yes	FN
Lymph nodes	Yes	No	FP
Liver	Yes	Yes	TP
Bones	No	No	TN
Lungs	Yes	Yes	TP

Specificity will be calculated using the following formula:

$$Specificity = \frac{TN}{TN + FP}$$

In the example above, ^{68}Ga-OPS202 PET/CT assessment will have a specificity equal to 0.5 when compared to SOT.

Subject-based and lesion-based sensitivity along with organ-based specificity will be summarised using descriptive statistics for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

It will be also summarised using descriptive statistics for following five radioactivity dose groups:

- ^{68}Ga-OPS202 PET/CT at 40 to 80 MBq
- ^{68}Ga-OPS202 PET/CT at 100 to 140 MBq
- ^{68}Ga-OPS202 PET/CT at 160 to 200 MBq
- ^{68}Ga-OPS202 PET/CT at 100 to 200 MBq *
- ^{68}Ga-OPS202 PET/CT at 40 to 200 MBq *

Note: *A subjects' scan will use either his visit 2 or visit 3 scan, and not both. ^{68}Ga-OPS202 PET/CT at (100-200 MBq) and (40-200 MBq) will use the same subjects except the scan/visit with the lowest dose will be read. i.e.

- For 100-200 MBq, will choose Arm: A visit3, B visit2, C visit 2
- For 40-200 MBq, will choose Arm: A visit2, B visit2, C visit 3

Individual values of subject-based, lesion-based sensitivity and organ-based specificity will be listed by subject and by visit for this assessment (PET/CT).

f) Comparison to sstr2 agonist positive scan results will be computed for sensitivity analysis

In order to compare ^{68}Ga-OPS202 PET/CT to sstr2 agonist PET assessments, the two following analyses will be performed:

- Sensitivity and specificity of previously acquired sstr2 agonist PET versus SOT.

Diagnostic sensitivity of previously acquired sstr2 agonist scan (at Visit 1) will be analysed by subject-based analysis and lesion-based approaches (per organ) compared to SOT.

Also, organ-based specificity will be computed.

Methodology for computing sensitivities and specificity will be same as described in e), with sstr2 PET instead of ^{68}Ga-OPS202 PET/CT assessments, compared to SOT.

As sstr2 agonist PET scan is performed only at Visit 1 and as SOT is not specific to V2 or V3, values of sensitivities/specificity will be unique per subject.

Subject-based and lesion-based sensitivity along with organ-based specificity will be summarised using descriptive statistics for all subjects.

Individual values of subject-based, lesion-based sensitivity and organ-based specificity will be listed by subject for this assessment (sstr2 PET).

- Comparison of sensitivity of ^{68}Ga-OPS202 PET/CT to previously acquired SSTR2 agonist PET.

The subject-based sensitivity of ^{68}Ga-OPS202 PET/CT will be compared to sensitivity of previously acquired SSTR2 agonist PET, both assessed vs SOT.

Therefore for each subject*visit, the difference will be computed as:

Sensitivity (PET/CT vs SOT) – Sensitivity (SSTR2 vs SOT).

Note that value of subject-based sensitivity (SSTR2 vs SOT) will be unique per subject.

This difference will be summarised using descriptive statistics for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

It will be also summarised using descriptive statistics for following five radioactivity dose groups:

- Difference of ^{68}Ga-OPS202 PET/CT (at 40 to 80 MBq) to SSTR2 PET
- Difference of ^{68}Ga-OPS202 PET/CT (at 100 to 140 MBq) to SSTR2 PET
- Difference of ^{68}Ga-OPS202 PET/CT (at 160 to 200 MBq) to SSTR2 PET
- Difference of ^{68}Ga-OPS202 PET/CT (at 100 to 200 MBq) to SSTR2 PET
- Difference of ^{68}Ga-OPS202 PET/CT (at 40 to 200 MBq) to SSTR2 PET

g) SUV_{max} ratio for lesions

For each PET assessment, lesion SUV_{max} will be measured for each of the most avid lesions identified per organ (up to a maximum of five most avid lesions per organ that are confirmed by SOT) and reported in the ICL database.

For each organ, the SUV_{max} ratio will be computed as follows:

$$SUV_{max}\ ratio\ = \frac{SUV_{max}}{SUV_{mean}\ \text{of the subject's reference tissue (tumour} - \text{free liver).}}$$

It will be analysed using descriptive statistics, presented for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

Individual values of SUV_{max} ratio will be listed by subject, by organ and by visit.

Background location will be specified (L: Liver, B = Aortic blood).

h) SNR in the liver

SNR will be calculated from lesion-free VOI (reference tissue) using following formula:

$$SNR = \frac{SUV_{mean}}{SUV_{SD}}$$

Those SUV_{mean} and SUV_{SD} will be available in the database provided by ICL.

A higher SNR in the liver indicates higher effectiveness of ^{68}Ga-OPS202 as a diagnostic agent.

It will be analysed using descriptive statistics, presented for:

- each of the six combinations of injected peptide/radioactivity dose range
- each of the two peptide mass dose ranges
- each of the three radioactivity dose ranges

Individual values of SNR in the liver will be listed by subject and by visit.

Background location will be specified (L: Liver, B = Aortic blood).

Additional listing:

A listing of SUV measurements by lesion and per organ will be provided, including following data listed by subject and by visit:

- Lesion SUV_{mean}
- Lesion SUV_{max}
- Lesion SUV_{max} ratio
- Lesion Tumour-to-background ratio

3.2.2 Safety

All safety data will be included in the data listings and summary tables will be based on the Safety population and presented by combination of injected peptide/radioactivity dose range and overall.

AEs will be allocated to each combination of injected peptide/radioactivity dose range following the following rule: AEs will be allocated to the last dose of ^{68}Ga-OPS202 received, based on AE start date/time.

Same rule will be applied for analysing concomitant medications, based on treatment start date/time.

For the safety parameters measured at each visit (ECG, laboratory data, vital signs, physical examinations), allocation to each combination of injected peptide/radioactivity dose range will follow the rule below:

- A unique baseline value will be defined per subject, as the last measurement collected prior to the first IIP administration
- For the post-baseline visits, assessments will be allocated to the last dose of ^{68}Ga-OPS202 received, based on date/time of assessment.

3.2.2.1 Adverse events

All AEs will be recorded and graded by investigators using the NCI CTCAE classification (Version 4.03, dated 14 June 2010), will be coded using the MedDRA Version 19.1 or higher, and will be classified by MedDRA PT and SOC.

Listings will be presented and sorted by combination of injected peptide/radioactivity dose range of ^{68}Ga-OPS202, subject number, start date of AEs, primary SOC, PT and verbatim text for all adverse events recorded during the study.

Listings of SAEs, AEs leading to IIP withdrawal and AEs leading to death (fatal outcome) will also be presented.

Also, a listing of grade ≥3 AEs will be provided.

Treatment Emergent Adverse Events (TEAEs) will be flagged (*) in the AE listings and will be summarised.

A TEAE is defined as any AE that occurs during the study if:

(1) it was not present prior to receiving the first ^{68}Ga-OPS202 injection, or

(2) it was present prior to receiving the first ^{68}Ga-OPS202 injection but the intensity increased during the study, or

(3) it was present prior to receiving the first ^{68}Ga-OPS202 injection, the intensity is the same but the causality became related during the study.

(4) AEs starting > 28 days after last ^{68}Ga-OPS202 injection will not be considered as TEAEs.

An overall summary table of all AEs will be presented by combination of injected peptide/radioactivity dose range and overall.

TEAEs will be summarised by combination of injected peptide/radioactivity dose range and overall with the number and percentage of subjects with adverse events classified by primary SOC and PT. The number of occurrences of a TEAE will also be presented.

In addition, summary tables will also be presented for SAEs, TEAEs by intensity and causality and TEAEs associated with withdrawals.

In the event of multiple occurrences of the same AE (same PT) being reported by the same subject, the maximum intensity (Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > missing > not applicable) and the most serious causality (related > missing > not related) will be chosen.

Nonetheless, for the table “Overall summary of adverse events”, in the cross classification of causality and intensity, any subject experiencing multiple AEs with different intensities for each causality category will be counted for each intensity.

3.2.2.2 Laboratory data

A separate listing of normal ranges for Standard International (SI) units will be provided by gender and age where relevant.

Laboratory data (serum haematology and biochemistry panels, urinalysis) will be listed in SI units and abnormal values will be flagged (high [H], low [L], clinically significant [C], NCI-CTC grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.

- Haematology and Biochemistry

For haematology and biochemistry parameters, the baseline will be defined as the last measurement collected prior to the first IIP administration.

For haematology and biochemistry parameters, summary statistics, by combination of injected peptide/radioactivity dose range and overall, will be presented at each scheduled assessment (Baseline, Post-dose, EOS/EW) for actual values and changes from baseline.

Shift tables for haematology and biochemistry parameters will be presented of the number and percentage of subjects with low, normal or high values.

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria, Version 4.03, dated 14 June 2010. The NCI CTC grade (0 to 4) of haematology and biochemistry by visit and by subject and will be listed in Section 16.2.8.

Listings of the laboratory parameters (as described in SAP Appendix 2 section 14.3.4) will include listings of NCI-CTC Grade 3 and 4 haematological toxicities, listings of NCI-CTC Grade 3 and 4 biochemical toxicities and listings of out of range biochemistry parameters that could not be graded using NCI-CTC grade (below Lower Limit of Normal range (LLN) – normal – above Upper Limit of Normal range (ULN).

Those listings will be presented by combination of injected peptide/radioactivity dose range, subject number and visit.

- Urinalysis

For categorical urinalysis data (absent/trace/positive of protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocyte esterase and glucose) frequency tables, by combination of injected peptide/radioactivity dose range, will be presented at each scheduled assessment (Baseline, post-dose, EOS/EW).

For continuous urinalysis data (pH and specific gravity), summary statistics, by combination of injected peptide/radioactivity dose range, will be presented at each scheduled assessment (Baseline, post-dose, EOS/EW) for actual values and changes from baseline.

3.2.2.3 Vital signs

Vital signs (body temperature, supine and standing blood pressure and heart rate, respiratory rate) and body weight will be listed by each assessment by combination of injected peptide/radioactivity dose range and subject. Any unscheduled vital signs will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the first IIP administration.

Summary statistics by combination of injected peptide/radioactivity dose range and overall will be presented at each scheduled assessment for actual values and changes from baseline.

Following assessment will be analysed: Baseline, 0.5h Post-dose, 1h Post-dose, 2h Post-dose, 4h Post-dose, EOS/EW.

3.2.2.4 ECG

ECG results will be listed at each assessment (Screening, EOS/EW) by combination of injected peptide/radioactivity dose range and subject. Any unscheduled ECG will be flagged [U] in the listings.

Baseline will be defined as the first ECG measurement collected prior to the first IIP administration.

For continuous ECG parameters (heart rate, RR duration, PR duration, QRS duration, QT duration, QTc Bazett, QTc Fridericia, QTc manual) summary statistics, by combination of injected peptide/radioactivity dose range and overall, will be presented at each scheduled assessment (EOS/EW) for actual values and changes from baseline.

For interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by combination of injected peptide/radioactivity dose range and overall, at each post-dose assessment (EOS/EW) as well as the changes from baseline with the following categories: improved, stable, worsened, clinically significant worsening.

3.2.2.5 Physical examination

Physical examination (normal, abnormal, specification for abnormal result) will be listed by combination of injected peptide/radioactivity dose range, subject number and visit. Any unscheduled physical examination will be flagged [U] in the listings.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

- Efficacy endpoints

No imputations will be made for missing data.

- Safety endpoints

If a value requires a retest (for laboratory values, vital signs, ECG), the closest non-missing reliable value to the scheduled visit is used in the summary tables. An assessment is considered reliable if it is performed without any technical problem or altered blood samples and if the result is within the range of plausible values.

Any repeat or additional assessments performed will be included in the individual subject data listings.

For AEs with missing information for the intensity and/or causality, the value will not be replaced and will be summarized as a separate category.

For all other variables, no imputations will be made for missing data.

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e., if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
- If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly a medication with partial start and stop dates could be considered as prior and concomitant treatment).
- Where possible, the derivations based on a partial date will be presented as superior inequalities (i.e., for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last administration will be "≥2". Similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

3.2.3.3 Outliers

Any outlier identified prior to database lock which is impossible/implausable will be excluded from the analysis. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

If any outliers are identified after database lock the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.

A search of outliers by Chiltern should be performed before the database lock and actions with the sponsor should be defined (e.g. edition of queries).

3.2.4 Subject disposition

The numbers and percentages of subjects included in each of the Screened, Randomised, Safety, PP and PK population will be tabulated in total and by randomisation arm. The reasons for subject exclusions from PP population will also be tabulated.

A listing of dates and time of assessments will be presented by subject for randomisation arm.

A summary table will be presented for each subject population presenting the number of subjects in each randomisation arm at each visit and identifying the number of subjects who withdrew from the study over time. A unique flow chart will be drawn with the number of subjects in each population.

3.2.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who completed and withdrew from the study and the reasons for withdrawal will be presented by randomisation arm and overall.

3.2.6 Demographic and baseline characteristics

In order to characterise the subjects, descriptive summary statistics (n, mean, SD, median, minimum, and maximum) or frequency counts of demographic and baseline data will be presented by randomisation arm (three sequences) and overall for the following populations:

- Randomised population
- PP population.

No statistical comparison of the randomisation arms will be performed.

Summary statistics will be provided for demographic and baseline characteristics:

- sex, race/ethnicity, age and age class
- height, weight at screening, body mass index (BMI) and BMI in categories at screening (refer to Appendix 1, Derived data)
- Eastern Cooperative Oncology Group (ECOG) performance status

Summary statistics of the tumour characteristics will be provided:

- site of primary tumour
- primary tumour resected
- time since diagnostic (refer to Appendix 1, Derived data)
- type of the tumour (functioning or non-functioning)
- tumour grade according to WHO 2010 classification
- differentiation status
- Tumour, node and metastasis (TNM) staging
- presence of metastases
- time since diagnostic of metastases (see refer to Appendix 1, Derived data)
- location of metastases

Summary statistics for the previous somatostatin receptor scan will be provided:

- time since scan (months)
- number of positive lesions (in total, in liver, in bone, in lymph nodes)

All demographic and baseline characteristics will be listed by randomisation arm and subject.

Pregnancy tests performed will be listed by randomisation arm, by subject, and by visit.

3.2.7 Medical and surgical history

Medical and surgical history will be coded using MedDRA Version 19.1 or higher.

Listings will present the PT and verbatim text. The listings will be sorted by randomisation arm, subject number, date of diagnosis, primary SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary SOC and PT for each randomisation arm and overall on the Randomised and PP population.

3.2.8 Prior Surgical Procedures for GEP-NETs

Prior surgical procedures for GEP-NETs will be tabulated and listed in a similar way to medical and surgical history.

3.2.9 Subject compliance

3.2.9.1 Subject exposure to IIP

Subject exposure to IIP will be described using a summary table by randomisation arm, for following data:

- Number of injections
- Exposure duration, as defined in Appendix 1 Derived data

Then, for each of the six combination of injected peptide/radioactivity dose range, a summary table will present the following information using descriptive statistics:

- Injected peptide mass dose (µg)
- Injected radioactivity dose (MBq)

Computational details for actual injected doses (peptide mass dose and radioactivity doses) are available in the Appendix 1 Derived data.

A first listing will present IIP preparation by subject and randomisation arm, with following information:

- Date and time of IIP preparation
- Final prepared volume (mL)
- Final prepared dose of radioactivity (MBq)
- IIP prepared as per protocol (yes/no with reason)

A second listing will be presented for IIP administration, by subject and randomisation arm, with following information:

- Administration performed to the subject (yes/no)
- Date and time of injection
- IIP and batch number
- Volume immediately before administration (ml)
- Radioactivity dose immediately before administration (MBq)
- Left over volume immediately after administration (mL)
- Left over radioactivity dose immediately after administration (MBq)
- Injected peptide mass dose (µg)
- Injected radioactivity doses (MBq)

Moreover, a listing of subjects with extravasation during injection or difficulties during IIP administration will be provided.

3.2.9.2 Subject compliance

For each subject, the overall compliance (%) will be calculated as the ratio of the actual number of injections over the planned number of injections, then multiplied by 100 (c.f. in Appendix 1 Derived Data).

A summary table of compliance by randomisation arm and overall will be presented on the Safety population, analysed as a continuous variable. Additionally, the number and percentage of subjects with a compliance in the categories (50% or 100%) will be provided by randomisation arm and overall.

3.2.10 Prior Medications for GEP-NETs

All prior treatments for the study disease will be recorded on the eCRF.

Prior medications for GEP-NETs will be coded using WHO Drug Dictionary (WHO-DD), version June 2016 or higher.

As defined in study protocol, following prior medications for GEP-NETs will be considered prohibited and will be flagged into listings:

- Within 28 days prior to the first 68Ga-OPS202 PET/CT exam (at Visit 2):
  - Long acting Somatostatin analogues (SSA), ie, Somatuline® Autogel® /Depot® (60, 90 or 120 mg) and Sandostatin® LAR (20 or 30 mg)
- Within 24 hours before first ^{68}Ga-OPS202 PET/CT (Visit 2 and Visit 3):
  - Short acting SSA (Sandostatin®)

Listings will be presented for the therapeutic class, PT and verbatim text. The listings will be sorted by randomisation arm, subject, chronological start date, stop date, therapeutic class, PT and verbatim text. The therapeutic class will correspond to the second level of Anatomical Therapeutic Chemical (ATC) code, which corresponds to the first three figures.

A frequency table of the number and percentage of subjects will be provided for all prior medications by therapeutic class and PT for each randomisation arm and overall on the Randomised and PP populations.

3.2.11 Prior and concomitant therapies

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.

All recorded data will be included in data listings.

As defined in study protocol, the following medications/therapies will be considered prohibited and will be flagged into listings:

- During the study and up to the second PET/CT scan and 48 hours post second OPS202 scan:
  - Administration of any radiopharmaceutical
  - Parenteral amino acid solutions and any formulation of diuretics on Visit 2 and Visit 3, unless stable adjusted diuretics for subjects with hypertension
- Within 28 days prior to the first 68Ga-OPS202 PET/CT exam (at Visit 2) and during the study up to Visit 3 after the second 68Ga-OPS202 PET/CT exam has been completed:
  - Long acting SSA, ie, Somatuline® Autogel® /Depot® (60, 90 or 120 mg) and Sandostatin® LAR (20 or 30 mg)
- Within 24 hours before each of the two ^{68}Ga-OPS202 PET/CT (Visit 2 and Visit 3):
  - Short acting SSA (Sandostatin®)

3.2.11.1 Prior and concomitant medications

Prior and concomitant medications will be coded using WHO-DD, version June 2016 or higher.

Medications that started and stopped before start of study treatment are considered as prior medications. Medications that started before start of study treatment, but are continuing will be considered as both prior and concomitant medications.

Listings will be presented for the therapeutic class, PT and verbatim text. The listings will be sorted by randomisation arm, subject number, chronological start date, stop date, therapeutic class, PT and verbatim text. The therapeutic class will correspond to the second level of ATC code, which corresponds to the first three figures.

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications by therapeutic class and PT for each randomisation arm and overall on the Randomised population.

3.2.11.2 Prior and concomitant non-drug therapies

Prior and concomitant non-drug therapies will be coded using the MedDRA Version 19.1 or higher. Therapies which started and stopped before start of study treatment are considered as prior non-drug therapies.

Therapies which started before start of study treatment but are continuing will be considered as both prior and concomitant non-drug therapies.

Listing of prior and concomitant non-drug therapies will be presented for the SOC, PT and verbatim text. The listing will be sorted by randomisation arm, subject number, chronological start date, stop date, SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided by SOC and PT for each randomisation arm and overall on the Randomised and PP populations.

3.2.11.3 Concomitant medications for GEP-NETs

Concomitant medications for GEP-NETs will be coded using WHO-DD, version June 2016 or higher. Medications which started and stopped before start of study treatment are considered as prior medications for GEP-NETs.

Medications which started before start of study treatment but are continuing will be considered as both prior and concomitant medications for GEP-NETs.

Listings will be presented for the therapeutic class, PT and verbatim text. The listings will be sorted by randomisation arm, subject number, chronological start date, stop date, therapeutic class, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided by therapeutic class and PT for each randomisation arm and overall on the Randomised and PP populations.

3.2.11.4 Concomitant surgical procedures

Concomitant surgical procedures will be coded using the MedDRA, Version 19.1 or higher. Surgical procedures which started after start of study treatment will be considered as concomitant surgical procedures.

Listings will be presented for the SOC, PT and verbatim text. The listings will be sorted by randomisation arm, subject number, chronological start date, stop date, SOC, PT and verbatim text.

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by SOC and PT for each randomisation arm and overall on the Randomised and PP populations.

3.2.12 Pharmacokinetics

Analysis of PK data by non-compartmental approach will be documented in a separate analysis plan under the responsibility of IPSEN Clinical Pharmacokinetics (Early Drug Development). As the time and date of PK samples will be collected in eCRF, Chiltern will provide a listing of PK sampling times, as well as any deviation from the scheduled time. A listing of individual OPS202 concentrations per timepoint should be provided.

3.2.13 Derived data

The derived data are variables which are calculated from the raw data recorded in the eCRF or any other support and not included in the database. The derived data will be calculated to be included in tables and listings. Some specifications of the data derivations necessary for this study are provided in Appendix 1 Derived Data.

3.2.14 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented n (number of non-missing observations), number of missing values (if any), arithmetic mean, standard deviation (SD), median and the range (minimum, maximum).

Mean, median and SD values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

For categorical or discrete variables, the absolute and relative (percentage) numbers based on the non-missing number of observations for each category will be presented.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population having non-missing values.

The denominator will be specified in a footnote to the tables for clarification if necessary.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such.

All text fields must be left justified and numeric or numeric with some text specification (e.g., not done, unknown, <4.5) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.15 Pooling of Centres

It is not planned to perform a subgroup analysis on individual or groups of centres.

3.2.16 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.

This interim analysis will be performed based on an interim database soft lock, as described in the Data Management Plan for the study.

Database soft lock will ensure data used for interim analysis are cleaned, coded and reconciled.

A subset of 25 subjects will be analysed for interim analysis, corresponding to all screened and randomised subjects until the achievement of a minimum of 12 evaluable subjects.

3.2.17 Covariates and analysis of subgroups

It is not planned to perform such analysis.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows 7.

4.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.2 or higher. All outputs will be in Microsoft Word Format, and delivered by the CRO as one single file per tables, listing, figure, and a compilation per ICH section.

4.3 Validation programs

SAS® programs are developed to produce clinical study output such as analysis data sets, summary tables, data listings, figures or statistical analyses. CCI [redacted] provides an overview of the development of such SAS® programs.

CCI [redacted] Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical study output by checking for their logic, efficiency and commenting, and by inspection of the produced outputs.

A Program Output Release form (CCI [redacted] will be prepared to document the methods of validation.

Copies of the QC documentation produced as confirmation that the validation process has been followed will be provided by Chiltern and will be retained by the sponsor.

4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, listings and statistical output along with associated logs will be given to the sponsor when the tables, listings, figures and statistical analysis has been finalised.

5 CHANGES FROM PROTOCOL

In relation to secondary efficacy criterion d) (Absolute number of lesions detected by ^{68}Ga-OPS202), analysis of the following parameters is included in the SAP while not explicit in the study protocol version 3.0:

- Number of subjects having lesions detected by ^{68}Ga-OPS202 when no lesions is detected by SOT (so called "False Positive" lesions, although in this instance, without histology, this determination is equivocal), in each of five anatomic sites (Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs).
- Number of subjects having lesions detected by SOT when no lesions is detected by ^{68}Ga-OPS202 (so called "False negative" lesions, although in this instance, without histology, this determination is equivocal), in each of five anatomic sites (Primary site of GEP-NET, Lymph nodes, Liver, Axial/appendicular skeleton (Bones), Lungs).

In relation to exploratory criterion g) (SUV_{max} ratio), the computation was modified comparing to study protocol. Protocol states that SUV ratio was computed by SUV_{max} lesion/ SUV_{max} reference tissue. Current SAP defines SUV_{max} ratio for each organ as SUV_{max} lesion divided by SUV_{mean} of subject's reference tissue (tumour-free liver).

In relation to definition of injected radioactivity dose (in SAP Appendix 1), the consideration of any extravasation in the computation was added.

In relation to adjustment for country/centre effect, protocol states that descriptive analysis will be carried out to describe any possible centre effect. Current SAP indicates that it is not planned to perform a subgroup analysis on individual or groups of centres.

In relation to primary efficacy variable analysis, descriptive statistics will not be tabulated by study arm but will be summarised for each of the six combinations of injected peptide/radioactivity dose range, presented in such a way that study arms are explicit, for each of the two peptide mass dose ranges and for each of the three radioactivity dose ranges.

In relation to key secondary efficacy variable analysis, descriptive statistics will not be tabulated by study arm but will be summarised for each of the six combinations of injected peptide/radioactivity dose range, presented in such a way that study arms are explicit, for each of the two peptide mass dose ranges and for each of the three radioactivity dose ranges.

6 REFERENCES

1 International Conference on Harmonisation (ICH) E9 Guidance on statistical principles for clinical trials. Federal register Vol 63, No. 179 (September 1998).

7 DATA PRESENTATION

Index and template of Tables, Listings and Figures are provided in Appendix 2.