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STATISTICAL AND ANALYSIS PLAN

PROTOCOL TITLE: AN INTERNATIONAL MULTI-CENTER, OPEN-LABEL STUDY TO EVALUATE SAFETY, TOLERABILITY, BIODISTRIBUTION, DOSIMETRY AND PRELIMINARY EFFICACY OF ^{177}LU-OPS201 FOR THE THERAPY OF SOMATOSTATIN RECEPTOR POSITIVE NEUROENDOCRINE TUMOURS

(NETs)

PROTOCOL VERSION AND DATE:
Version 10.0 – 10 August 2020

SAP Version	Date
Version 1.0 - Final	29 March 2017
Version 1.1 – Draft	28 June 2019
Version 1.2 Draft	23 July 2019
Version 1.3 Draft	12 August 2019
Version 2.0 – Final	21 November 2019
Version 2.1 Final	24 March 2020
Version 3.0 Final	17 November 2020
Version 4.0 Final	17 March 2021
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STUDY NUMBER:	OPS-C-001 / D-FR-01072-001
EUDRACT NUMBER	2015-002867-41
PROTOCOL TITLE:	AN INTERNATIONAL MULTI-CENTER, OPEN-LABEL STUDY TO EVALUATE SAFETY, TOLERABILITY, BIODISTRIBUTION, DOSIMETRY AND PRELIMINARY EFFICACY OF ^{177}LU-OPS201 FOR THE THERAPY OF SOMATOSTATIN RECEPTOR POSITIVE NEUROENDOCRINE TUMOURS (NETS)
SAP VERSION:	Version 4.1 – Final
SAP DATE:	09 July 2021

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
Statistician	PPD IPSEN	eSignature	
Medical Development Director	PPD Ipsen Biopharm Ltd	eSignature	

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study statistician	PPD Covance Clinical	eSignature	
Manager statistician	PPD Covance Clinical	eSignature	

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
Version	Section	Was	Is	
Final 1.0	All SAP	29 Mar 2017	21 November 2019	Update according to protocol amendment 9 (previous version was linked to amendment 4)
Final 2.0	All SAP	21 November 2019	24 March 2020	Update to add analyses for efficacy and PK
Final 3.0	All SAP	24 March 2020	17 November 2020	Main edits to address key changes to amendment 10 of the protocol
Final 4.0	All SAP	17 November 2020	17 March 2021	Updates following Dry-Run comments.
Final 4.1	All SAP	17 March 2021	09 July 2021	RFS update + Table numbering error correction.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
ADL:	Activity of Daily Living
AE:	Adverse Event/Experience
Ae	Amount excreted
ALT (SGPT):	Alanine aminotransferase
AP:	Alkaline phosphatase
AST (SGOT):	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Chemical
AUC:	Area Under the Curve
BMI:	Body Mass Index
BOR:	Best Overall Response
Bq:	Becquerel
BSA:	Body Surface Area
ceCT:	contrast enhanced Computer Tomography
CI:	Confidence Interval
Cl_R	Renal clearance of the drug from plasma
CR:	Complete Response
CRF:	Case Report Form
CRO:	Contract Research Organisation
CRP:	C-Reactive Protein
CT:	Computer Tomography
CT/MRI:	Computer Tomography/Magnetic Resonance Imaging
CTC:	Common Toxicity Criteria
CTCAE:	Common Terminology Criteria for Adverse Events
CV:	Coefficient of Variation
DCR:	Disease Control Rate
DLT:	Dose Limiting Toxicity
DM:	Data Management
DNA:	DeoxyriboNucleic Acid
e:	Electronic
EANM:	European Association of Nuclear Medicine
ECG:	Electrocardiogram
eCRF:	Electronic Case Report Form

ABBREVIATION	Wording Definition
eGFR:	estimated Glomerular Filtration Rate
EOCT:	End of Core-Trial
EOLTFU:	End of Long-term Follow-up
EORTC:	European Organisation for Research and Treatment of Cancer
EW:	Early Withdrawal
FAS:	Full Analysis Set
FDA:	Food and Drug Administration
f_e	Fraction of the intravenously administered drug excreted into the urine
fT4:	free Thyroxine
FU:	Follow-Up
GBq:	GigaBecquerel
GEP NET:	GastroEnteroPancreatic NeuroEndocrine Tumour
GGT:	Gamma-Glutamyl Transferase
GI.NET:	GastroIntestinal NeuroEndocrine Tumour
Gy:	Gray, SI unit of absorbed radiation dose
h:	hour(s)
HPF:	High Power Field
IA:	Injected radioactivity
IA / ROI:	Injected radioactivity/Region Of Interest
ICH:	International Conference on Harmonisation
IGF-1:	Insulin-like Growth Factor 1
IRPP:	Investigational Radiopharmaceutical Product
IRPPD:	Investigational Radiopharmaceutical Product Dossier
ITT:	Intention-To-Treat
ITT-DAS:	Intention-To-Treat Dosimetry Analysis Set
i.v.:	Intravenous
L:	litre
LLN:	Lower Limit of Normality
MBq:	MegaBecquerel
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
min:	minute(s)

ABBREVIATION	Wording Definition
MIRD:	Medical Internal Radiation Dose
mL:	millilitre
MRI:	Magnetic Resonance Imaging
NCI:	National Cancer Institute
NCI-CTC:	National Cancer Institute – Common Toxicity Criteria
NCI-CTCAE:	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCRNPD:	Non-Complete Response/Non-Progressive Disease
NE:	Not Evaluable
NET:	NeuroEndocrine Tumour
ORR:	Overall Response Rate
PD:	Progressive Disease
PET/CT:	Positron Emission Tomography/Computed Tomography
PFS:	Progression Free Survival
PK:	Pharmacokinetic
PP:	Per Protocol
PP-DAS:	Per Protocol Dosimetry Analysis Set
PR:	Partial Response
PRRT:	Peptide Receptor Radionuclide Therapy
PV:	Pharmacovigilance
QC:	Quality Control
QLQ:	Quality of Life Questionnaire
QoL:	Quality of Life
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
SAP:	Statistical Analysis Plan
SAS:	Safety Analysis Set
RECIST:	Response Evaluation Criteria in Solid Tumours
ROI:	Region Of Interest
SAE:	Serious Adverse Event
SAS:	Safety Analysis Set
SAS®:	Statistical Analysis System®

ABBREVIATION	Wording Definition
SD:	Stable Disease
SI:	Standard International
SOP:	Standard Operating Procedure
SPECT:	Single Photon Emission Computer Tomography
SPECT/CT:	Single Photon Emission Computer Tomography/ Computer Tomography
SRC:	Safety Review Committee
SRS:	Somatostatin Receptor Scan
Sv:	Sievert
TEAE:	Treatment Emergent Adverse Event
TFLs:	Tables, Figures and Listings
TPR:	Time Point Response
TSH:	Thyroid Stimulating Hormone
ULN:	Upper Limit of Normality
WHO:	World Health Organization
WHO- DD:	World Health Organization – Drug dictionary
µg:	Microgram
^{68}Ga:	Positron-emitting isotope of Gallium
^{177}Lu:	^{177}Lutetium
^{177}Lu-IPN01072:	Study medication, ^{177}Lu-labeled somatostatin antagonist for Peptide Receptor Radionuclide Therapy
^{177}Lu-OPS201:	Study medication, ^{177}Lu-labeled somatostatin antagonist for Peptide Receptor Radionuclide Therapy

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

The primary objective of this Phase I/II study is to assess the safety and tolerability of Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-OPS201 administered in three cycles in subjects with somatostatin receptor (sstr) 2 positive neuroendocrine tumours (NETs) (including phaechromocytomas and paragangliomas).

1.1.2 Secondary objectives

This study also aims to achieve the following secondary objectives:

- To evaluate the optimal radioactivity and peptide mass dose to be used in future studies
- To characterise ^{177}Lu-OPS201 whole body biodistribution and pharmacokinetics (PK) of the radiopharmaceutical after each administration of ^{177}Lu-OPS201.
- To determine the radiation dosimetry of ^{177}Lu-OPS201 (organ exposure to administered radioactivity) after each administration of ^{177}Lu-OPS201 with three different peptide mass doses.
- To undertake a preliminary assessment of the therapeutic efficacy of ^{177}Lu-OPS201 PRRT by determination of Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 status.
- To evaluate the influence of ^{177}Lu-OPS201 PRRT on the subject´s Quality of Life.

1.1.3 Exploratory objectives

CCI [redacted]

- To determine the PK of OPS201 in plasma and urine;

CCI [redacted]

1.2 Study design

1.2.1 General description

This is an open-label study to evaluate the safety and tolerability of ^{177}Lu-OPS201 for the treatment of NETs. This international, multicentre study is planned to be conducted in approximately 20 sites with distinguished experience in PRRT or comparable nuclear medicinal applications in Europe, USA and Australia.

The study will be performed in two parts, Part A and Part B.

A total of up to 55 subjects with histologically confirmed diagnosis of GEP NETs, lung NETs or pheochromocytoma or paraganglioma will be recruited in the trial:

- Part A: a minimum of 6 subjects and up to 15 subjects;
- Part B: a minimum of 25 subjects and up to 40 subjects.

Eligible subjects will receive three administrations (or up to 5 cycles in part B) of ^{177}Lu-OPS201 at 8-week intervals (+2 weeks, or up to +4 weeks in case of AEs which have not adequately recovered)

Subject safety and dose escalation (before initiating Part B) will be evaluated by an SRC in Part A and a DRB (Part B).

The overall study design is shown in Figure 1, Figure 2 (Part A) and Figure 3 (Part B).

After signing informed consent, subjects will undergo screening (Screening Visit) up to 4 weeks before the first administration of ^{177}Lu-OPS201 to check enrolment eligibility criteria. A contrast enhanced CT/MRI (baseline for RECIST v1.1 evaluation) will be performed and a screening Somatostatin Receptor Scan (SRS) will also be performed (unless already performed within 6 months prior to Visit 1 Day 1). Eligibility read for SRS and CT/MRI will be performed locally at screening. However, all images, including SRS, will be sent to the imaging core laboratory for later evaluation.

Although the visits are similar in Part A and Part B, there is a change in the amendment version 6.0 in the CT/MRI imaging which only affects Part B, hence visits for Part A and B are described separately. In both Part A and Part B, the end of the core study is defined as the EOCT Visit of the last subject.

During the study, subjects will attend the following visits:

Part A

Visit 1: On Visit 1 Day 1, subjects will receive the first administration of ^{177}Lu-OPS201 followed by safety and extended dosimetry evaluations over 8 days, with additional laboratory safety tests repeated at Day 15 (±2 days). At 4 weeks (±5 days) after Visit 1 Day 1 (i.e. Follow-up Visit 1), the safety of the subjects will be assessed.

Visit 2: 8 weeks after Visit 1 Day 1 (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered) subjects will receive the second administration of ^{177}Lu-OPS201 followed by safety and dosimetry evaluations over 8 days, with additional laboratory safety repeated at Day 15 (±2 days). At 4 weeks (±5 days) after Visit 2 Day 1 (Follow-up Visit 2), the safety of the subjects will be assessed. Additionally, subjects will receive a CT/MRI to monitor the RECIST v1.1 status and tumour volume changes.

Visit 3: 8 weeks after Visit 2 Day 1 (+2 weeks or up to+4 weeks in case of AEs which have not adequately recovered), subjects will receive the third administration of ^{177}Lu-OPS201 followed by safety and dosimetry evaluations over 8 days, with additional laboratory safety tests repeated at Day 15 (±2 days). At 4 weeks (±5 days) after Visit 3 Day 1 (Follow-up Visit 3), the safety of the subjects will be monitored.

EOCT Visit: 8 weeks (±5 days) after Visit 3 Day 1, the safety and efficacy of the treatment will be evaluated. Subjects enrolled in Part A after the protocol version (v6.0) comes into effect will receive a CT/MRI scan to monitor the RECIST v1.1 status and tumour volume.

Part B

Visit 1: On Visit 1 Day 1, subjects will receive the first administration of ^{177}Lu-OPS201 followed by safety and extended dosimetry evaluations over 8 days, with additional laboratory safety tests repeated at Day 15 (±2 days). At Week 4 (Day 29±5 days), Week 6 (Day 42±5 days) (i.e. Follow-up Visit 1) and at the intermediate timepoints, the safety of the subjects will be assessed.

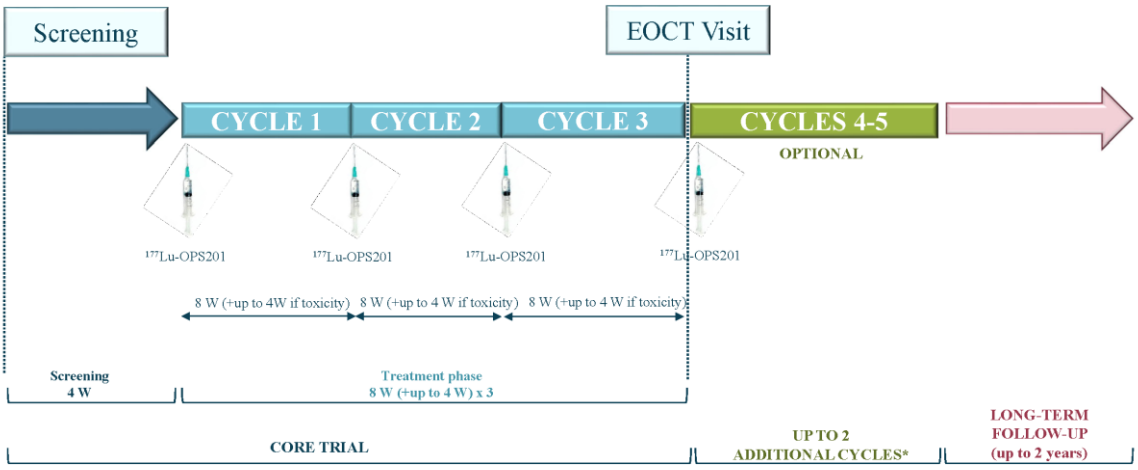
Visit 2: 8 weeks after Visit 1 Day 1 (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered) subjects will receive a CT/MRI scan to monitor the RECIST v1.1 status and tumour volume. Subjects will then receive the second administration of ^{177}Lu-OPS201 followed by safety and dosimetry evaluations over 8 days, with additional laboratory safety test repeated at Day 15 (±2 days). At Week 4 (Day 29±5 days) Week 6 (Day 42±5 days) (Follow-up Visit 2) and at intermediate timepoints, the safety of the subjects will be assessed.

Visit 3: 8 weeks after Visit 2 Day 1 (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered), subjects will receive a CT/MRI scan to monitor the RECIST v1.1 status and tumour volume. Subjects will then receive the third administration of ^{177}Lu-OPS201 followed by safety and dosimetry evaluations over 8 days, with additional laboratory safety test repeated at Day 15 (±2 days). At Week 4 (Day 29±5 days) Week 6 (Day 42±5 days) (Follow-up Visit 3) and at intermediate timepoints, the safety of the subjects will be monitored.

EOCT Visit: 8 weeks (±5 days) after Visit 3 Day 1, the safety and efficacy of the treatment will be evaluated. Subjects will receive a CT/MRI scan to monitor the RECIST v1.1 status and tumour volume.

Subjects who are to receive additional cycles of therapy will undergo the EOCT assessment after Cycle 3. Where possible, the EOCT visit and Visit 4, Day 1 of the first additional cycle can be combined.

Figure 1 Overview of Study Design for Part A and Part B and Post Study Follow-up



EOCT=end of core trial; W=weeks, * Only for Part B.

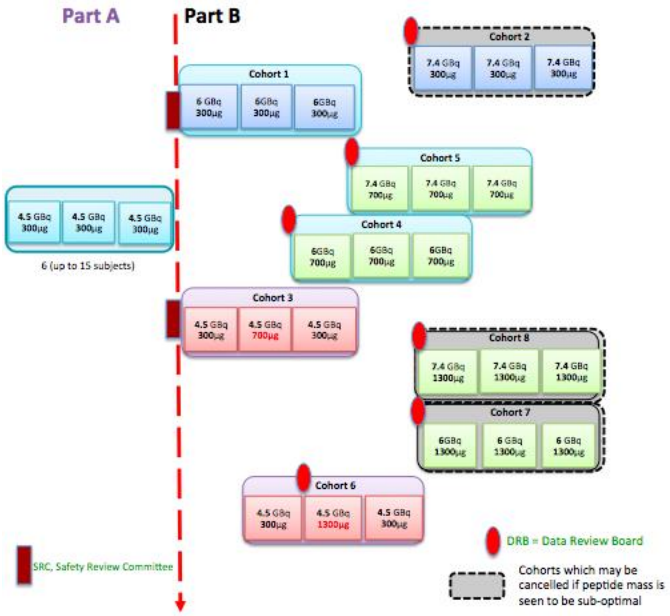
1.2.1.1 Part A Design

In Part A, it is planned to treat up to 15 subjects with three cycles of 4.5 GBq ^{177}Lu-OPS201. An SRC will decide, based on the dosimetry and safety data of the initial three and then

six subjects, if the remaining nine subjects will continue at the same radioactivity level or if the radioactivity has to be adapted. Alternatively, Part A can be closed and Part B initiated.

Figure 2 shows the study design for Part A.

Figure 2 Study Design- Part A



1.2.1.2 Part B Design

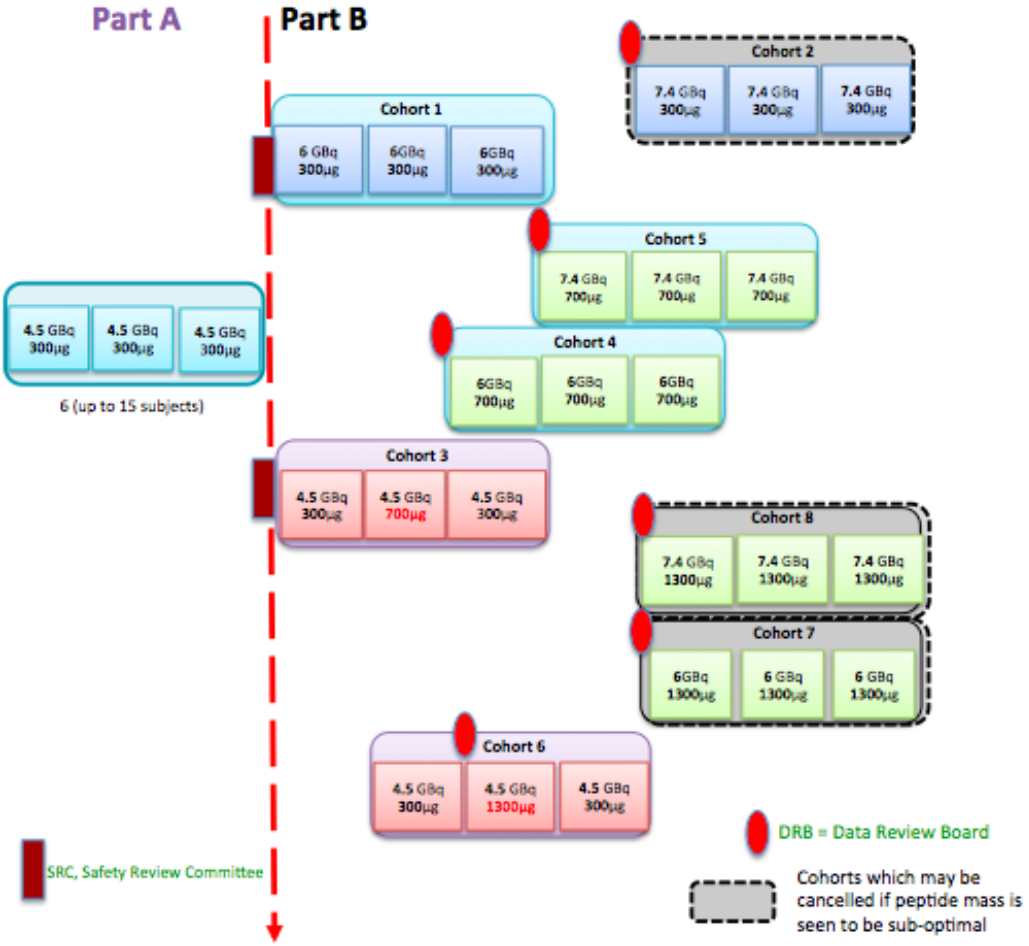
Part B is a dose escalation both of peptide mass and radioactivity. Up to eight cohorts will be enrolled as described below, see Figure 3.

Part B will encompass radioactivity and peptide mass dose escalation as well as intra-individual peptide mass dose evaluation. It consists of up to eight cohorts. In each cohort, each subject will receive three cycles of the defined radioactivity and peptide mass dose of ^{177}Lu-OPS201 (see Table 1). Each cycle will be 8 (+2) weeks apart. In case of AEs which are not adequately recovered, a further 4 weeks can be added between dosing.

After the first three core-treatment cycles, up to two additional cycles of ^{177}Lu-OPS201 can be administered if the subject continues to meet the criteria outlined in Section 1.3.1.3 and the subject has clinical benefit (defined as CR, PR or SD). The additional cycles are optional and must be discussed with the sponsor before administration.

The population of Cohorts 3 and 6 will enrol eight to 10 subjects to ensure a minimum of eight completed subjects. All remaining cohorts (1, 2, 4, 5, 7 and 8) will enrol three to five subjects to ensure a minimum of three completed subjects per cohort. A completed subject is defined as one who has received at least 3 cycles of study treatment or fewer than 3 cycles if one of the following has occurred: exceedance of organ dose limits, treatment-related safety issues or disease progression.

Figure 3 Study Design- Part B



DRB=Data Review Board; GBq=gigaBecquerel; SRC=safety review committee.
Each cohort consists of three cycles of treatment. Cohort 2 will not be conducted if 700 µg or 1300 µg peptide mass is shown to be optimal. Cohorts 7 and 8 will not be conducted if 1300 µg peptide mass is seen to be too high. Cohorts 3 and 6 require 10 subjects for eight to be completed. All other cohorts are three to five subjects (minimum of three subjects to be completed).

1.2.2 Long-term Follow-up

The long-term follow-up period will start after the EOCT/end of additional cycles (EOAC)/early withdrawal (EW) Visit.

Tumour assessments will be performed every 3 months (±2 weeks) until whichever occurs first: documented disease progression (radiological or clinical as per investigator's judgement), 2 years after the EOCT/EOAC/EW Visit, withdrawal of consent, lost to follow-up or death.

Safety assessments and the subject's status will be assessed every 3 months (±2 weeks) until whichever occurs first: 2 years after the EOCT/EOAC/EW Visit, withdrawal of consent, lost to follow-up or death.

After the long-term follow-up period is completed i.e. 2 years after the EOCT/EOAC/EW Visit, all subjects will be invited to participate in a safety surveillance study, as part of a separate study protocol. All subjects will be asked to sign a new informed consent form to enter this study. The purpose of the safety surveillance study is to monitor any long-term effects of ^{177}Lu-OPS201 up to 5 years from the first dose of ^{177}Lu-OPS201.

Extra visits, examinations, tests and interventions can be performed at any time if clinically indicated, as judged by the investigator.

1.2.3 Additional Optional Cycles Part B

If a subject tolerates the treatment well and shows clinical benefit (e.g. CR, PR, or SD) up to two additional cycles at a radioactivity dose adjusted based on dosimetry results can be administered to this subject provided limiting organ absorbed dose levels have not been exceeded. Two cycles would consist of ^{177}Lu-OPS201 administration every 8 weeks (+2 weeks, or plus up to 4 weeks in case of AEs which are not adequately recovered) with administration of the same peptide mass dose as Cycle 1. In this case, subjects will have the same assessments as during the core treatment cycles and up to EOAC or early withdrawal except for exploratory biomarkers CCI . Dosimetry will thus be performed after each additional cycle to prevent exceeding limiting organ absorbed doses. For these subjects, an EOAC visit will be done 8 weeks (±5 days) after the last ^{177}Lu-OPS201 dose administration. In this case, the 2-year long-term follow-up will start at the EOAC (instead of EOCT).

The decision to administer additional cycles or any other antitumoural treatment is at the investigator's and subject's discretions and must be discussed with and confirmed by the sponsor. However, the investigator should follow the following rules before proceeding to any additional administration:

- subjects with Dose Limiting Toxicities (DLTs) after first, second or third administration will be discontinued from ^{177}Lu-OPS201.
- subject will be eligible for an additional administration of ^{177}Lu-OPS201 only if:
  - renal function and blood cell counts are in the range defined in the study inclusion criteria (#12 and #13), within the treatment cycle.
  - cumulative organ absorbed doses did not exceed 1.5 Gy in BM and 23 Gy in kidneys.
  - subject is likely to benefit from additional cycles of ^{177}Lu-OPS201 therapy.

The planned maintenance dose for any cycle may be adjusted such that the limiting organ absorbed doses are not exceeded.

Subjects who are to receive additional cycles of therapy will undergo the EOCT assessment after Cycle 3. Where possible, the EOCT visit and Visit 4, Day 1 of the first additional cycle can be combined. An additional EOAC assessment will be done 8 weeks after the last dose of therapy.

1.2.4 Study population

A total of up to 55 subjects with histologically confirmed diagnosis of GEP NETs, lung NETs or pheochromocytoma or paraganglioma will be recruited in the trial:

• Part A: a minimum of 6 subjects and up to 15 subjects;

• Part B: a minimum of 25 subjects and up to 40 subjects.

It is intended that potential subjects for this study will be identified from those currently attending or being referred to the study centres for the diagnosis and treatment of NETs including phaeochromocytomas and paraganglioma. Potentially suitable subjects will be approached by the investigating team to ascertain whether they would be interested in participating in the study. Interested subjects will be provided with an information sheet and undergo consenting procedures prior to any other study procedures. If a subject initially fails the Screening process due to a reversible condition, the Screening can potentially be repeated once at a later time point (re-enrolment).

1.2.5 Study duration

The estimated core trial duration of Part A is 18 to 21 months (for all subjects) including 6 to 10 months of treatment for a single subject, while the long-term follow-up lasts for up to 2 years after the EOCT/EW Visit.

The estimated core trial duration of Part B is 14 to 20 months (for all subjects) including 6 to 10 months of treatment for a single subject, while the long-term follow-up will last for up to 2 years after the EOCT/EOAC/EW Visit.

1.3 Methods and procedures

1.3.1 Study treatment

1.3.1.1 Treatment of subjects

Subjects will be treated with three cycles and may receive up to 2 additional cycles (Part B only) of ^{177}Lu-OPS201 PRRT with an interval of 8 weeks +2 weeks, or up to +4 weeks in case of AEs which have not adequately recovered. If any side effects are adequately recovered within the 4 weeks, the next treatment cycle can be initiated; if not, no further PRRT treatment will be administered and the subject will undergo the EOCT (or EOAC) Visit followed by the Long-term Follow-up Visits.

The absorbed organ doses (blood and image based), especially the bone marrow and kidney doses as a limiting organs, will be analysed after each treatment cycle so that the radioactivity for the following cycles for this particular subject can be reduced in order to not exceed cumulative absorbed organ dose limits.

1.3.1.2 Study drugs administered

The study will be performed in two parts.

Part A (15 subjects)

Initially, six subjects will be treated. Each subject will receive three cycles of 4.5 GBq (target radioactivity 4.5 GBq±10%) ^{177}Lu-OPS201 (target dose 300±50 µg), every 8 weeks (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered). An SRC meeting will be held before exposing the remaining nine subjects to the entire number of planned administrations.

Part B (up to 40 subjects)

The following table provides the specific radioactivity and peptide mass dose for each cohort in Part B.

Table 1 Radioactivity and Peptide Mass Dose in Each Cohort and Cycle – Part B

Cohorts	Planned dose escalation			
	Nominal OPS201 dose per cycle (µg)	OPS201 range per cycle (µg)[a]	Nominal radioactivity and range (GBq)	Cumulative radioactivity (3 cycles, GBq)
1	300	[250 to 350]	6.0±10%	18.0
2[b]	300	[250 to 350]	7.4±10%	22.2
3	300 (Cycle 1) 700 (Cycle 2) 300 (Cycle 3) 300 (Cycle 4 and 5)[c]	[250 to 350] [550 to 850] [250 to 350] [250 to 350]	4.5±10%	13.5
4	700	[550 to 850]	6.0±10%	18.0
5	700	[550 to 850]	7.4±10%	22.2
6	300 (Cycle 1) 1300 (Cycle 2) 300 (Cycle 3) 300 (Cycle 4 and 5)[c]	[250 to 350] [1100 to 1500] [250 to 350] [250 to 350]	4.5±10%	13.5
7[b]	1300	[1100 to 1500]	6.0±10%	18.0
8[b]	1300	[1100 to 1500]	7.4±10%	22.2

DOTA=tetraxetan; GBq=gigaBecquerel; IRPP=investigational radiopharmaceutical product; OP201=somatostatin analogue peptide JR11 coupled to DOTA.

a IRPP will be provided either through local or centralised manufacturing. OPS201 ranges include the ranges validated for local IRPP manufacturing in radiopharmacy of selected centres and the general validated range for centralised IRPP manufacturing (i.e. nominal OPS201 dose±15%).

b optional.

c For additional cycles, if any

At each PRRT cycle, the study medication will be administered after the conduct of a safety examination of the subject. The IRPP (20 mL of ^{177}Lu-OPS201) will be administered once per cycle by an i.v. infusion at a rate of 10 mL/h over 120 minutes. Infusion rate modification (up or down) would be under the investigator's judgement and may be temporarily halted or even further slowed down if the subject does not tolerate the IRPP infusion. The overall infusion duration should not exceed 4 hours.

Prophylaxis may be considered if the subject is thought to be at increased risk of infusion-related reactions as per the site's standard of care. Appropriate treatment should be administered should an infusion-related reaction occur including somatostatin analogues. At any time, if infusion-related reactions are encountered, the infusion should be slowed or interrupted.

There are no fasting conditions, nor food restrictions that should apply when administering ^{177}Lu-OPS201 to the subject.

1.3.1.3 Delay of administration and withdrawal from treatment

Part A

If any of the following occur, no further ^{177}Lu-OPS201 treatment will be administered:

- Subject withdraws his/her consent to further treatment
- Cumulative kidney dose exceeds 23 Gy
- Cumulative bone marrow dose exceeds 1.5 Gy as determined by image based dosimetry
- Absolute neutrophil count < $1.000*10^9$ /L (i.e. Grade 3 or higher)
- Platelets < $50.0*10^9$ /L (i.e. Grade 3 or higher)

- If one of the following medical conditions occurs (based on CTCAE v5.0) and does not resolve within 4 weeks (resolved=toxicity Grade 2 or lower and is at the discretion of the investigator):
  - Estimated glomerular filtration rate (eGFR) of < 45mL/min
  - Liver function tests (total bilirubin, aminotransferases) higher than Grade 3 (unless there is treatment-related liver toxicity, in which case the study treatment should be stopped or interrupted to enable recovery when deterioration of the liver function is noted);
  - Any other adverse event above Grade 2, except hair loss

The investigator can decide at his/her discretion to discontinue the treatment or to reduce the administered radioactivity for further safety reason than those here listed above to prevent a patient from higher grade toxicity.

Before the administration of Cycles 2 and 3 these criteria must be checked. In the event of withdrawal (discontinuation) from treatment only the Early Withdrawal (EW) Visit and the Long-term Follow-up will be performed (with the EW Visit 8 weeks after the last administration of 177Lu-OPS201).

In some cases, cumulative absorbed dose to the bone marrow or kidney may be difficult to evaluate. If there is uncertainty about the radiation dose received to critical organs, but without substantial toxicity, the decision to administer additional cycles is left at the investigator's and subject's discretions. The decision may be either to stop the treatment, administer the full dose or a reduced dose depending on the benefit-risk balance for the subject.

In the situation of persisting Grade 3 and higher bone marrow, toxicity, a bone marrow aspirate can be considered if at the discretion of the investigator this could contribute to the evaluation of the event.

Part B

If any of the following occur, no further ^{177}Lu-OPS201 treatment will be administered:

- subject withdraws his/her consent to further treatment;
- cumulative kidney dose exceeds 23 Gy;
- cumulative bone marrow dose exceeds 1.5 Gy, as determined by image-based dosimetry;
- platelets <50.0*10^9/L (i.e. Grade 3 or higher);
- if one of the following medical conditions occurs (based on CTCAE v5.0 criteria,) and does not resolve within 4 weeks (resolved=toxicity Grade 1 or recovered, and is at the discretion of the investigator):
  - eGFR of <45 mL/min/1.73m2;
  - liver function tests (total bilirubin, aminotransferases, alkaline phosphatase and gamma glutamyl transferase (GGT) higher than Grade 3 (unless there is treatment-related liver toxicity, in which case the study treatment should be stopped or interrupted to enable recovery when deterioration of the liver function is noted);
  - any other related AE above Grade 2, except hair loss, lymphopenia, nonfebrile neutropenia lasting <4 weeks.

The investigator can decide at his/her discretion to discontinue the treatment or to reduce the administered radioactivity for further safety reason than those here listed above to prevent a subject from higher grade toxicity.

Before the administration of Cycles 2 and 3 these criteria must be checked. In the event of withdrawal (discontinuation) from treatment only the EW Visit and the long-term follow-up will be performed (with the EW Visit, 8 weeks after the last administration of ^{177}Lu-OPS201). In some cases, absorbed dose to the bone marrow or kidney may be difficult to evaluate. If there is uncertainty about the radiation dose received to critical organs, but without substantial toxicity, the decision to administer additional cycles is based on continuing to meet requirements of the inclusion criteria, the investigator's judgement and subject's discretion. The decision may be either to stop the treatment, administer the full dose or a reduced dose depending on the benefit-risk balance for the subject.

In the situation of persisting Grade 3 and higher bone marrow toxicity, a bone marrow aspirate can be considered, at the discretion of the investigator, if this could contribute to the evaluation of the event.

1.3.2 Efficacy assessments

The following secondary efficacy variables will be assessed:

- Objective tumour response based on RECIST v1.1 (CT/MRI scan) by calculating BOR, ORR and DCR
- Progression free survival (PFS) based on RECISIT v1.1 (CT/MRI)
- Influence of ^{177}Lu-OPS201 PRRT on Quality of Life of the Subjects based on change in Quality of Life Questionnaire (QLQ)-C30; GI.NET21) from baseline to EOCT.

CCI

Evaluation of tumour change in volume from baseline to EOCT/EOAC/EW based on sstr2 positive lesions

Efficacy imaging endpoints will be assessed locally by the investigator up to the end of the 2-year long-term follow-up period and by the central imaging laboratory up to the EOCT/EOAC/EW Visit.

CCI

CCI

1.3.2.1 Contrast Enhanced CT Imaging/MRI

Sites will be provided with a study manual including the submission procedures and the imaging acquisition guidelines. Tumour response assessments will be performed on-site (locally) and off-site (centrally, during the core trial period and additional cycles only). CT/MRI images will be used for the tumour response assessments (RECIST v1.1 and other endpoints). An imaging charter will be prepared detailing the independent read set-up and the read methodology. The imaging charter will also include the methodology for the eligibility read.

Radiological assessments for tumour response will be performed at the Screening Visit, repeated at each cycle of therapy, at the EOCT /EOAC /EW Visit, and every 3 months during the 2-year follow-up period or at any time. Additionally, in the event of biological or clinical signs of disease progression further radiological assessments can be made based upon investigator's judgment.

The screening tumour assessments will include pelvis, chest and abdomen, and will be performed within 1 month before Visit 1 Day 1. If a historic CT/MRI scan is present that is not older than 1 month at Visit 1 Day 1, this scan can be used. However, the site should ensure that all required anatomies are covered and perform scanning for missing anatomies. Imaging parameters used at screening should remain consistent throughout the study. Follow-up imaging should include chest, pelvis and abdomen. The chest should be included if lesions were present at screening.

For chest/abdomen/pelvic scans, the scan should extend from the lateral ends of the clavicles (to ensure complete coverage of lung apices) down to the lesser trochanters or caudally thereof (to ensure complete coverage of inguinal lymph nodes). For abdomen/pelvic scans, the scan should begin cranially at the right dome of the diaphragm and extend down to the lesser trochanters or caudally thereof (to ensure complete coverage of inguinal lymph nodes). Details for image acquisition and provision for central review will be given in a separate imaging charter.

During the Treatment Period (Core Trial and additional cycles in Part B) and the 2-year long-term follow-up period, ^{68}Ga-PET scans can be performed, if deemed necessary by the investigator.

1.3.2.2 Evaluation of Tumour Response

Tumour response will be evaluated by the site investigator and by an independent central review. The central review will be the data used for all imaging efficacy endpoints. Response and progression will be evaluated using the revised RECIST guideline (v1.1) and CCI [redacted]. Only subjects with measurable disease at baseline, who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and permit reproducible repeated measurements. On occasion, if the largest lesion does not permit reproducible measurement, the next largest lesion which can be measured reproducibly will be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are included in the sum, then only the short axis will be added into the sum. The baseline sum of diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including any measurable lesions over and above the five target lesions should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each should be noted throughout follow-up.

Overall objective tumour response will be classified as CR, PR, SD or PD, and unevaluable according to RECIST v1.1 at each visit. Based on objective tumour response, BOR, ORR, DoR and DCRwill be calculated for both the central and the investigator review.

Time to PFS according to RECIST v1.1 will also be summarised.

Details of the response evaluation will be given in a separate image review charter.

CCI

1.3.2.3 Quality of Life Questionnaire - QoL

A Quality of Life Questionnaire, composed of a general questionnaire for oncological subjects (QLQ C30; 28 items with a 4-point scale and two items with a scale from one to seven) and a NET-specific questionnaire (Gl.NET21; 20 items with a 4-point scale) in paper-form will be completed at baseline (Visit 1, predose), during treatment at Visits 2 and 3 (predose), and at the EOCT /EOAC /EW Visit. It is important that the investigator does not influence the subject's responses to the questionnaire in any way.

1.3.3 Safety assessments

1.3.3.1 Adverse Events

Adverse events are defined as any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

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

By definition, all AEs are regarded as 'treatment emergent', i.e. not seen before treatment or, if already present before treatment, worsened after start of treatment.

Natural progression or deterioration of NETs including symptoms or malignancy under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE. Death due to disease progression will be recorded as part of the efficacy evaluation and will not be regarded as an SAE. Neuroendocrine tumour status will be monitored through RECIST v1.1 evaluation and completion of Quality of Life Questionnaires (QLQ C-30 and GINET.21). Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of NETs (symptoms/malignancy). These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgment) if they are:

- Judged by the investigator to be unusually severe or accelerated NETs or;
- If the investigator considers the deterioration of NETs signs and symptoms to be caused directly by the IRPP or OPS301 if applicable.

If there is any uncertainty about an AE being due solely to the NETs under study, it should be reported as an AE/SAE as appropriate. Preplanned or elective surgeries or therapies should be recorded in the subject's source documents but are not to be considered AEs unless there was any change to the subject's medical condition during the AE collection period.

All AEs will be assessed and documented in the eCRF by the investigator. Follow-up of the AE, after the last visit of the trial, 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.

Preplanned or elective surgeries or therapies should be recorded in the subject's source documents but are not to be considered AEs unless there was any change to the subject's medical condition during the AE collection period.

All AEs (including SAEs) are to be accurately recorded on the AE page of the subject's Case Report Form (CRF).

For both serious and non-serious AEs, documentation must be supported by an entry in the patient's hospital notes. The following information should be captured for all AEs: date of onset and resolution, severity of the event, assessment whether the event was serious or non-serious, Investigator's opinion of the relationship to investigational drug (OPS201 or OPS301), treatment required for the AE, action taken with IRPP or OPS301 if applicable, and information regarding resolution/outcome.

Each event will be graded for severity using the classifications of CTCAE v5.0. For events not addressed in the CTCAE v5.0 (as appropriate), classifications the following grading will apply:

- Mild (Grade 1) - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2) - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL).
- Severe (Grade 3) - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated.
- Death (Grade 5) related to AE.

The relationship of an AE to IRPP 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 IRPP 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 IRPP administration.

The relationship of the study treatment to an AE will be determined by the investigator and subsequently reviewed by the sponsor.

1.3.3.2 Serious Adverse Events

An SAE is classified as any untoward medical occurrence that at any dose:

- Results in death, or;
- 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, or;
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further), or;
- Results in persistent or significant disability / incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions, or;
- Is a congenital anomaly / birth defect in the offspring of a subject who received the IRPP or OPS301 if applicable;
- 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 in-patient 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 safety database. This includes any suspected or confirmed coronavirus COVID-19 (SARS-CoV-2) infection (seriousness criteria should be “other medically significant” if no other seriousness criteria are present (e.g. hospitalisation).

Planned hospitalisations that occur exclusively for study procedures must not be documented as SAEs.

1.3.3.3 Clinical Laboratory Tests

The certified laboratory of the study site will perform haematology, biochemistry and urinalysis laboratory tests. Pituitary markers will be analysed at local laboratory unless this assessment cannot be performed locally, it will be analysed in a central laboratory. CCI [redacted] A copy of the laboratory certification and tabulation of the reference ranges will be provided.

1.3.3.3.1 Hematology

Haematology parameters include haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, white blood cell count (total and differential: leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes), red blood cells and platelets.

Haematology will be measured at the Screening Visit, at Visits 1 to 3 and optional Visits 4 and 5 (predosing, 24±1 hour (Day 2), 48±1 hour (Day 3), 72 to 96 hours (Day 4 to 5), 144 to 168 hours (Day 7 to 8) and Day 15±2 days), Follow-up Visits, the EOCT/EOAC/EW Visit and the visits in the 2-year long-term follow-up period.

1.3.3.3.2 Blood Biochemistry

Biochemistry parameters include sodium, potassium, chloride, calcium, glucose, creatinine, urea, albumin, total bilirubin, AST, ALT, alkaline phosphatase, GGT, C-reactive protein. Creatinine clearance will also be calculated.

The eGFR value will be calculated by the Modification of Diet in Renal Disease (MDRD) formula.

Biochemistry will be measured at the Screening Visit, at Visits 1 to 3 and optional Visits 4 and 5 (predosing, 24±1 hour (Day 2), 48±1 hour (Day 3), 72 to 96 hours (Day 4 to 5), 144 to 168 hours (Day 7 to 8) and Day 15±2 days), Follow-up Visits, the EOCT/EOAC/EW Visit and the visits in the 2-year long-term follow-up period.

1.3.3.3.3 Urinalysis

Urinalysis parameters include specific gravity, pH, protein, glucose, blood, urobilinogen, erythrocytes, leukocytes, ketones, bilirubin, nitrite, albumin.

To be measured at the Screening Visit, predose and Day 15 at Visits 1 to 3 and optional Visits 4 and 5, Day 7 to 8 at Visit 1, at Follow-up Visits 1 to 3, at the EOCT/EOAC/EW Visit, and at the visits in the 2-year long-term follow-up period.

1.3.3.3.4 Pregnancy test

Prior to each PRRT cycle (Screening Visit, Visits 1 to 3 and optional Visits 4 and 5, predosing) each female subject of childbearing potential must undergo a pregnancy test. A serum pregnancy test will be performed at the Screening Visit. A serum or urine pregnancy test will be performed predose on Day 1 of Visits 1 to 3.

In the event of pregnancy, the subject is not allowed to receive further PRRT cycles and must be withdrawn from the study. The pregnancy must be reported to the sponsor on the SAE form until the end of the trial.

1.3.3.3.5 Pituitary Marker (Marker of Pituitary Function)

Pituitary markers include free thyroxine (fT4), cortisol, insulin-like growth factor (IGF)-1 and thyroid stimulating hormone (TSH). These markers results will not be included in the summary statistics if subjects are receiving substitute or therapy concerning the respective pituitary axis (e.g. no analysis of fT4 and TSH in subjects who receive thyroxine, no analysis of cortisol in subjects who received corticosteroids).

Measured predose at Visit 1, Day 1 at 08:00 (±1 hour) and Visit 1, Day 2 – important to judge cortisol value, and at the EOCT/ EOAC/EW Visit.

1.3.3.4 Physical Examination

A physical examination (including examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, musculoskeletal, cardiovascular and nervous systems) will be carried out by a physician at Screening and each study visit up to, and including, the EOCT/EOAC/EW Visit and the visits in the 2-year long-term follow-up period. Any clinically significant abnormalities at Screening will be noted on the medical history pages of the eCRF. During the study, if in the opinion of the investigator there are any clinically significant changes in the physical examination findings (abnormalities), they will be recorded as AEs.

1.3.3.5 Height and Weight

Subject height will be measured at the Screening Visit, while weight will be assessed pre-dose at Visits 1-3 (and optional Visits 4 and 5) and at the EOCT/EOAC/EW Visit. Body surface area (BSA) will be determined with the Mosteller formula [2].

Height and weight and associated calculated parameters, will be summarised together with the vital signs.

1.3.3.6 Vital Signs

Body temperature and supine vital signs (blood pressure and heart rate) will be measured on the nondominant arm after 5 minutes of supine rest at the following time points: at the Screening Visit, at Visits 1 to 3 and optional Visits 4 and 5 (predose, postinfusion: at stop of infusion (0), 30±5 minutes, 60±10 minutes, 4 hours ±10 minutes, 24±1 hour (with the exception of Visit 1: 08:00/Day 2 corresponds approximately 18 to 20 hours), 48±1 hour (Day 3), 72 to 96 hours (Day 4 to 5), 144 to 168 hours (Day 7 to 8), Day 15, Follow-up Visits, the EOCT/EOAC/EW Visit and the visits in the 2-year long-term follow-up period.

1.3.3.7 Electrocardiography

A 12–lead ECG will be performed at the Screening Visit, predose at Visits 1 to 3 and optional Visits 4 and 5, at the Follow-up Visits, at the EOCT/EOAC/EW Visit and at the visits in the 2-year long-term follow-up period. ECGs will be recorded in triplicate and in the supine position after at least 5 minutes of rest.

During the administration of the PRRT study drug, starting with the injection of the antiemetic (i.e. 15 to 30 minutes before the start of the amino acid infusion), a 24 hour ECG (Holter) will be recorded to monitor cardiac safety during the treatment.

The site will be required to review ECGs as a safety check at each Day 1 before administration. This will be done immediately by a qualified investigator at the study site. ECG and Holter assessments will be reviewed centrally during the core trial period and local review at the site will be performed during visits in the 2-year long-term follow-up period. Results will be provided to the site and retained as source data.

1.3.3.8 Performance Status

The performance status of the subjects will be defined by the Karnofsky scoring and assessed at the Screening Visit, pre-dose at Visits 1-3, pre-dose at optional Visits 4-5 and at the EOCT/EOAC/EW Visit.

- 100 - Normal; no complaints; no evidence of disease,

- 90 - Able to carry on normal activity; minor signs or symptoms of disease,
- 80 - Normal activity with effort; some signs or symptoms of disease,
- 70 - Cares for self; unable to carry on normal activity or to do active work,
- 60 - Requires occasional assistance but is able to care for most of his personal needs,
- 50 - Requires considerable assistance and frequent medical care,
- 40 - Disabled; requires special care and assistance,
- 30 - Severely disabled; hospital admission is indicated although death not imminent,
- 20 - Very sick; hospital admission necessary; active supportive treatment necessary,
- 10 - Moribund; fatal processes progressing rapidly,
- 0 – Dead.

1.3.3.9 Subject Demographics

At the Screening Visit the following demographic data will be collected: year of birth, sex, childbearing potential, and ethnicity.

1.3.3.10 Medical History

Relevant medical history will be recorded in the eCRF at the Screening Visit and includes diagnosis and assessments of any current medical condition, especially details of the NET diagnosis and prior cancer therapies (e.g. previous surgery, chemotherapy, radiotherapy, SSA use), and concomitant health conditions. In case of SAEs, medical history should also be reported in the SAE form.

1.3.3.11 Prior and Concomitant Medication

Prior medications/therapies will be reported if taken up to 28 days prior to the Screening Visit. Concomitant medications/therapies will be reported at every visit throughout the core trial and additional optional cycles. Any effort to report prior NET treatment/therapy prior to study entry will be reported. The only treatments recorded during the Long-term Follow-up period will be further antitumour treatments for NETs. In case of SAEs, concomitant medications should also be reported in the SAE form.

1.3.4 Pharmacokinetics assessments

1.3.4.1 Pharmacokinetics of the Radiopharmaceutical

1.3.4.1.1 Blood Sample Collection

For each subject, total radioactivity concentration in whole blood will be measured. Each subject will have blood samples (2 mL) taken as follows:

Visit 1:

- Before infusion, at stop of infusion (0), 5 minutes ±1 minute, 30 minutes±3 minutes, 1 hour±5 minutes, 4 hours±10 minutes, 24±1 hours, 48±1 hours, 72 to 96 hours, and 144 to 168 hours after the stop of infusion.

Visits 2 and 3:

- Before infusion, at stop of infusion (0), 1 hour±5 minutes, 4 hours±10 minutes, 24±1 hour, 48±1 hour, 72 to 96 hours and 144 to 168 hours.

For subjects receiving additional administrations (up to two additional cycles, Part B only), blood samples will be taken at each cycle according to the timepoints described above for Visits 2 and 3.

Blood samples should be collected from the contralateral arm used for the study drug infusion, or from another anatomical site.

The accurate time of sample collection and the accurate time of measurement of the radioactivity concentration must be recorded.

1.3.4.1.2 Urine Sample Collection

To determine the renal excretion of ^{177}Lu, urine will be collected during the first 48 hours post infusion at the following time period:

Visit 1 only:

- **Part A**: from the start of the infusion to 6 hours, 6 to 24 hours, 24 to 48 hours postinfusion
- **Part B**: from the start of the infusion to 4 hours, 4 to 24 hours, 24 to 48 hours (from the start of the infusion to 4 hours postinfusion only for US and Canada sites)

The accurate time of urine collection, time of radioactivity measurement and the total urine volume must be accurately recorded for each collection interval.

1.3.4.1.3 Analytical Procedures

Total radioactivity concentration in whole blood and urine will be determined on site/locally using a gamma counter calibrated for ^{177}Lu according to the dosimetry operational manual (DOM). The time of the sample collection and the time of measurement of the radioactivity concentration must be recorded.

1.3.4.2 Nuclear Medicine Imaging for Dosimetry

1.3.4.2.1 Whole Body Scan

To determine the biokinetics, whole body scans (planar scintigraphy) will be obtained 4 hours±10 minutes, 24±1 hour, 48±1 hour, 72 to 96 hours and 144 to 168 hours, after the start of the ^{177}Lu-OPS201 administration at Visits 1 to 3.

For subjects receiving additional administrations (up to two additional cycles, Part B only), dosimetry assessments will be performed after each additional administration with nuclear medicine imaging described above.

1.3.4.2.2 SPECT/CT Scan

Part A

For absolute quantification, additional three-dimensional (3D) SPECT/CT will be obtained at 24 hours±1 hour at Visits 1 to 3. It is mandatory for a valid quantification, that the SPECT/CT is calibrated.

Part B

For absolute quantification, 3D SPECT/CT will be obtained at 4 hours±10 minutes, 24±1 hour, 48±1 hour, 72 to 96 hours and 144 to 168 hours, after the start of the ^{177}Lu-OPS201 administration at Visits 1 to 3.

For subjects receiving additional administrations (up to two additional cycles, Part B only), dosimetry assessments will be performed after each additional administration with nuclear medicine imaging described above.

1.3.4.3 Pharmacokinetics of the OPS201

1.3.4.3.1 Blood Sample Collection

Part B only. Blood samples (2 mL) for assessment of OPS201 plasma levels will be collected at the following time points (at Visit 1 only):

At Visit 1 (first infusion): before the infusion (baseline), at the end of the infusion (0), 5±1 minute, 30±3 minutes, 60±5 minutes and at 4 hours±10 minutes, 6 hours±30 minutes, 8 hours ±30 minutes ,24±1 hours and 48±1 hours after the administration of ^{177}Lu-OPS201. Earlier versions of the protocol may have used other timepoints.

Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site.

The accurate time of sample collection must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

1.3.4.3.2 Urine Sample Collection

To determine the renal excretion of OPS201, the concentration of OPS201 in urine will be determined.

The samples for urine OPS201 concentration analysis will be taken from urine collected during three different periods at Cycle 1 only: from 0(start of the infusion) to 4, 4 to 24 and 24 to 48 hours after the start of infusion (0 (start of the infusion) to 4 hours only for US and Canada sites).

The accurate time of urine collection and the total urine volume for each collection interval must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

1.3.4.3.3 Analytical Procedures

Plasma and urine samples will be analysed to determine concentrations of OPS201 using a high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection, according to a separate protocol established with the dedicated analytical laboratory.

CCI [redacted] This could include protein binding analysis, metabolite profiling or analysis of excipients. Plasma and urine samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long-term stability, reproducibility).

CCI [redacted]

CCI [redacted]

CCI

[redacted]

1.3.5 Withdrawal/discontinuation

Since this is a therapeutic study, subjects will be considered to have completed the core-study when the final visit of the study treatment period (EOCT Visit) is completed.

Subjects may decide to withdraw from the study at any time and for any reason without prejudice to their further medical care. The Investigator may withdraw a patient from the treatment or the study for any of the following reasons:

- *Safety Reason/Adverse Event*: Clinical or laboratory events occurred that in the medical judgment of the Investigator, for the best interest of the subject are reasons for discontinuation. This includes serious and non-serious AEs regardless of relation to study medication.
- *Disease Progression*: The Investigator documents disease progression (based on RECIST v 1.1 or clinical symptoms) and does not expect any beneficial effect of the continuation of the study treatment.
- *Protocol Deviation*: The subject's findings or conduct failed to meet the Protocol entry criteria or failed to adhere to the Protocol requirements (e.g. drug non-compliance, failure to return for defined number of visits) as judged by the Investigator or Sponsor. The violation necessitated premature termination from the study.
- *Withdrawal of Consent*: The subject wished to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the CRF.
- *Lost to Follow-Up*: The subject stopped coming for visits, and study personnel were unable to contact the subject.
- Other: Any other reasons.

In the event of pregnancy, the patient is not allowed to receive further PRRT cycles and must be withdrawn from the study.

The Sponsor reserves the right to request the withdrawal of a patient due to protocol deviation or other significant reason.

Although a subject is not obliged to give reason(s) for withdrawing, if a subject is discontinued at any time after entering the study, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights. The investigator will make every effort to contact the subject and complete the termination status page on the eCRF and if possible conduct an EW Visit that will take place 8 weeks after the last administration study medication. In case of discontinuation of treatment/withdrawal from treatment, the EW Visit and the Long-term Follow-up Visits will be performed as planned.

The reasons for treatment and/or study discontinuation should be collected.

Appropriate follow-up of withdrawn subjects will be performed, as required. Attempts to contact subjects who withdraw from a study must be documented.

Withdrawn patients will be replaced if they do not complete treatment (the first three cycles) due to any reason other than exceedance of organ dose limits, treatment-related safety issues or disease progression.

1.3.6 Schedule of assessments

The schedule of assessments is provided in the study flow chart in Table 2 for Part A and Table 3 for Part B.

Extra visits, examinations, tests and interventions can be performed at any time if clinically indicated, as judged by the Investigator.

If the COVID-19 pandemic prevents subjects from coming to the site, subjects can have their study visit assessments performed remotely as judged appropriate by the investigator. This must be discussed with the sponsor before being implemented. In such a case, the investigator will perform a telemedicine visit and will make every effort, where applicable, to contact the subject's general practitioner or specialist physician to ensure all important medical information and safety event(s) occurring since the last visit are collected. Guidance on how to collect protocol-planned assessments will be provided to the investigator in a separate document. This document will be filed in the electronic trial master file. IECs/IRBs will be notified of the changes as applicable locally. Of note, as the adapted visit deviates from the regular protocol plan, the changes will be recorded as protocol deviations related to COVID-19.

Table 2 Study Procedures and Assessments Part A

	Screening Visit	Visit 1						FU Visit 1	Visits 2/3						FU Visits 2 + 3[a]	End of Core Trial Visit/ EW Visit[b]	LTFU Visits (up to 2 years)
	Week -4 to -1	Day 1	Day 2	Day 3	Day4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)		
Study informed consent	x																
Inclusion/Exclusion criteria check	x																
Subject demographics	x																
Medical history	x																
Prior/Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[c]
Pregnancy test [d]	x	x[e]							x[e]								
Physical examination	x	x[e]						x	x[e]						x	x	x
Height* and weight**	x*	x**[e]							x**[e]							x**	
ECG (12-lead)	x	x[e]						x	x[e]						x	x	x
24 hour ECG (Holter)		x[f]							x[f]								
Vital signs	x	x[g]	x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x	x
Performance status	x	x[e]							x[e]							x	
Quality of Life Questionnaire		x[e]							x[e]							x	
Haematology/Biochemistry	x	x[e]	x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x	x
CCI [redacted]																	
Pituitary markers		x[e]	x													x	
Urinalysis	x	x[e]				x	x	x	x[e]					x	x	x	x
CCI [redacted]																	
CT/MRI	x[o]														x[n]	x	x[p]
Somatostatin receptor scan	x[q]																
Whole body scan		x	x	x	x	x			x	x	x	x	x				
SPECT/CT			x							x							
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[r]
Survival		x						x	x						x	x	x
^{177}Lu-OPS201 infusion		x							x								

	Screening Visit	Visit 1						FU Visit 1	Visits 2/3						FU Visits 2 + 3[a]	End of Core Trial Visit/ EW Visit[b]	LTFU Visits (up to 2 years)
	Week -4 to -1	Day 1	Day 2	Day 3	Day4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)		

CT=computed tomography; DNA=deoxyribonucleic acid; DOTA=tetraxetan; ECG=electrocardiogram; EOCT=end of core trial; EW=early withdrawal; FU=follow-up; LTFU=long-term follow-up; ^{177}Lu=lutetium-177; MRI=magnetic resonance imaging; OPS201=somatostatin analogue peptide JR11 coupled to DOTA; PK=pharmacokinetics; RNA=ribonucleic acid; SPECT=single photon emission computed tomography; SRS=somatostatin receptor scintigraphy; TAC=time-activity curve.

a follow-up Visit 2 takes place 4 weeks after Visit 2 Day 1; Follow-up Visit 3 takes place 4 weeks after Visit 3 Day 1. Before the administration of Cycles 2 and 3 the criteria in Section 11.3 must be checked. In the event of withdrawal (discontinuation) from treatment the EOCT Visit and the Long-term Follow-up Visits will be performed as planned with the EOCT Visit, 8 weeks after the last administration of ^{177}Lu-OPS201.

b The Early Withdrawal Visit will take place 8 weeks after the last administration study medication.

c during Long-term Follow-up, only antitumour treatments for NETs will be recorded.

d a serum pregnancy test will be performed at the Screening Visit. A serum or urine pregnancy test will be performed predose on Day 1 of Visits 1 to 3

e predosing: safety assessment results must be checked before ^{177}Lu-OPS201 administration (with the exception of Quality of Life); these can be performed one day before administration.

f 24-hour ECG (Holter) to start 15 to 30 minutes before the amino acid infusion.

g prior to infusion and at infusion completion (0), 30±5 min, 60±10 min, 4 hours ±10 min after the end of ^{177}Lu-OPS201 infusion.

h blood sampling to determine TACs will be performed before the infusion (baseline), at the stop of infusion (0), 5, 30 minutes, 1, 4, 24, 48, 72 to 96 and 144 to 168 hours after the stop of infusion of ^{177}Lu-OPS201 (Visit 1). Blood sampling for Visits 2 and 3 will be performed before the infusion (baseline), at the stop of infusion (0), 1, 4, 24, 48, 72 to 96 hours and 144 to 168 hours postinfusion.

i urine will be collected for the following time periods: Visit 1 only: 0 to 6 hours, 6 to 24 hours, and 24 to 48 hours postinfusion.

j in selected sites only.

CCI

n at Follow-up Visit 2 only.

o ceCT/MRI not older than 1 month on Visit1 Day 1.

p central read of ceCT/MRI is performed during Core Trial and local read is performed during the 2-year LTFU period. ^{68}Ga-PET scan may be performed during the Core Trial and the 2-year LTFU period, if deemed necessary by the investigator.

q sstr scan should be performed (unless already performed within 6 months prior to Day 1) Local SRS eligibility read is performed at screening.

r up to 6 months after the last study drug administration, all AEs/SAEs will be collected unless new NET therapies are started, then only AEs/SAEs related to the study drug/procedure will be collected. From 6 months after the last study drug administration until 2 years after the EOCT/EOAC/EW Visit, withdrawal of consent, lost to follow-up or death, all AEs/SAEs related to the study drug/procedure will be collected.

Table 3 Study Procedures and Assessments Part B

	Screening Visit	Visit 1						FU Visit 1		Visits 2/3 + additional optional V4, V5[v]						FU Visits 2 + 3 + additional optional V4, V5[a]				
	Week -4 to -1	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	EOCT/EW Visit during the Core Trial (±5 days) [b]	EOAC/EW Visit during additional cycles [b] [v]	LTFU Visits (up to 2 years)
Study informed consent	x																			
Inclusion/Exclusion criteria check	x																			
Subject demographics	x																			
Medical history	x																			
Prior/Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[c]
Pregnancy test[d]	x	x[e]								x[e]										
Physical examination	x	x[e]						x		x[e]						x		x	x	x
Height* and weight**	x*	x**[e]								x**[e]								x**	x**	
ECG (12-lead)	x	x[e]						x		x[e]						x		x	x	x
24 hour ECG (Holter)		x[f]								x[f]										
Vital signs	x	x[g]	x	x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x	x	x	x
Performance status	x	x[e]								x[e]								x	x	
Quality of Life Questionnaire		x[e]								x[e]								x	x	
Haematology/Biochemistry	x	x[e]	x	x	x	x	x	x	x	x[e]	x	x	x	x	x	x	x	x	x	x
CCI	[redacted]																			
Pituitary markers		x[e]	x															x	x	
Urinalysis	x	x[e]				x	x	x	x	x[e]					x	x	x	x	x	x
Radioactive PK and dosimetry[h][ı]		x	x	x	x	x				x	x	x	x	x						

	Screening Visit	Visit 1						FU Visit 1		Visits 2/3 + additional optional V4, V5[v]						FU Visits 2 + 3 + additional optional V4, V5[a]				
	Week -4 to -1	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	EOCT/EW Visit during the Core Trial (±5 days) [b]	EOAC/EW Visit during additional cycles [b] [v]	LTFU Visits (up to 2 years)
CCI																				
OPS201 PK[l] [m]		x	x	x																
Tumour biopsy[n] (optional)	x															x[o]				
CCI																				
CT/MRI	x[r]									x								x	x	x[s]
Somatostatin receptor scan	x[t]																			
Whole body scan		x[u]	x	x	x	x				x	x	x	x	x						
SPECT/CT		x	x	x	x	x				x	x	x	x	x						
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [w]
Survival		x						x		x						x		x	x	x
^{177}Lu-OPS201 infusion		x								x										

	Screening Visit	Visit 1						FU Visit 1		Visits 2/3 + additional optional V4, V5[v]						FU Visits 2 + 3 + additional optional V4, V5[a]				
	Week -4 to -1	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	EOCT/EW Visit during the Core Trial (±5 days) [b]	EOAC/EW Visit during additional cycles [b] [v]	LTFU Visits (up to 2 years)

CT=computed tomography; DNA=deoxyribonucleic acid; DOTA=tetraxetan; ECG=electrocardiogram; EOCT=end of core trial; FU=follow-up; ^{177}Lu=lutetium-177; LTFU=long-term follow-up; MRI=magnetic resonance imaging; OPS201=somatostatin analogue peptide JR11 coupled to DOTA; PK=pharmacokinetics; RNA=ribonucleic acid; SPECT=single photon emission computed tomography; SRS=somatostatin receptor scintigraphy; TAC=time-activity curve.

a follow-up Visits take place 4 weeks and 6 weeks after administration of ^{177}Lu-OPS201 at Day 1. Before the administration of Cycles 2 and 3 (and additional optional Cycles 4 and 5) the criteria in Section 6.4.2 must be checked. In the event of withdrawal from treatment, the EW Visit will be performed 8 weeks after the last administration of ^{177}Lu-OPS201 and the LTFU visits will be performed as planned after the EOCT/EOAC/EW Visit. Additional tests in the presence of toxicity are to be done as clinically indicated.

b Subjects who are to receive additional cycles of therapy will undergo the EOCT assessment after Cycle 3. Where possible, the EOCT visit and Visit 4, Day 1 (additional cycle) can be combined. An additional EOAC assessment will be done 8 weeks after the last dose of therapy. The EW Visit will take place 8 weeks after the last administration study medication.

c during Long-term Follow-up, only antitumour treatments for NETs will be recorded.

d a serum pregnancy test will be performed at the Screening Visit. A serum or urine pregnancy test will be performed predose on Day 1 of Visits 1 to 3

e predosing: safety assessment results must be checked before ^{177}Lu-OPS201 administration (with the exception of Quality of Life); these can be performed one day before administration.

f 24-hour ECG (Holter) to start 15 to 30 minutes before the amino acid infusion.

g prior to infusion and at infusion completion (0), 30±5 min, 60±10 min, 4 hours ±10 min after the end of ^{177}Lu-OPS201 infusion.

h urine will be collected for the following time periods: Visit 1 only: 0 (start of the infusion) to 4 hours, 4 to 24 hours, and 24 to 48 hours postinfusion (only 0 (start of the infusion) to 4 hours for US and Canada sites).

i blood sampling to determine TACs will be performed before the infusion (baseline), at the stop of infusion (0), 5, 30 minutes, 1, 4, 24, 48, 72 to 96 and 144 to 168 hours after the stop of infusion of ^{177}Lu-OPS201 (Visit 1). Blood sampling for Visits 2 and 3 will be performed before the infusion (baseline), at the stop of infusion (0), 1, 4, 24, 48, 72 to 96 hours and 144 to168 hours postinfusion.

j in selected sites only.

CCI [redacted]

l blood samples for assessment of OPS201 plasma levels will be collected at Visit 1 (first infusion): before the infusion (baseline), at the end of the infusion (0), 5±1 minute, 30±3 minutes, 60±5 minutes and at 4 hours±10 minutes, 6 hours±30 minutes, 8 hours ±30 minutes, 24±1 hours and 48±1 hours after the administration of ^{177}Lu-OPS201.

m Urine samples for assessment of OPS201 urine levels will be collected Visit 1 only at the following time periods: 0 (start of the infusion) to 4 hours, 4 to 24 hours, and 24 to 48 hours postinfusion (only 0 (start of the infusion) to 4 hours in US and Canada sites).

CCI [redacted]

o at Follow-up Visit 2 only.

p at baseline (before the infusion)

CCI [redacted]

r ceCT/MRI not older than 1 month on Visit 1 Day 1. To be performed also at each cycle of therapy (+2 weeks or up to +4 weeks in case of AEs), at the EOCT/EOAC/EW visit (±5 days) and at each long-term follow-up visit (±2 weeks)

	Screening Visit	Visit 1						FU Visit 1		Visits 2/3 + additional optional V4, V5[v]						FU Visits 2 + 3 + additional optional V4, V5[a]				
	Week -4 to -1	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	Day 1	Day 2	Day 3	Day 4 to 5	Day 7 to 8	Day 15 (±2 days)	Day 29 (±5 days)	Day 42 (±5 days)	EOCT/EW Visit during the Core Trial (±5 days) [b]	EOAC/EW Visit during additional cycles [b] [v]	LTFU Visits (up to 2 years)

s central read of ceCT/MRI is performed during Core Trial and additional optional cycles; local read is performed during the 2-year LTFU period. ^{68}Ga-PET scan may be performed during the treatment period (Core Trial and Additional Cycles) and the 2-year LTFU period, if deemed necessary by the investigator.

t sstr scan should be performed (unless already performed within 6 months prior to Day 1) Local SRS eligibility read is performed at screening.

u postdosing imaging at 4 hours ±10 min. In case of misadministration (such as spillage or interruption of the infusion), an additional whole body scan is required shortly after the end of infusion and before the first bladder emptying (see Section 9.2.1 Whole Body Scan).

v at additional optional Visit 4 and Visit 5, no samples for pituitary markers, biobanking and exploratory biomarkers will be collected, except those for tumour markers. At the EOAC/EW Visit during additional cycles, no samples for biobanking and exploratory biomarkers will be collected, except those for tumour markers, and pituitary markers.

w up to 6 months after the last study drug administration, all AEs/SAEs will be collected unless new NET therapies are started, then only AEs/SAEs related to the study drug/procedure will be collected. From 6 months after the last study drug administration until 2 years after the EOCT/EOAC/EW Visit, withdrawal of consent, lost to follow-up or death, all AEs/SAEs related to the study drug/procedure will be collected.

1.3.7 Planned sample size

It is anticipated that a total of up to 55 subjects will be recruited. 15 subjects in Part A and 40 subjects in Part B. This is considered appropriate for an exploratory study and it is not based on formal statistical sample size calculation. In the event subjects do not complete treatment due to any reasons other than exceedance of organ dose limits or treatment-related safety issues, additional subjects will be recruited as replacements to ensure an adequate sample size in the "per protocol set" for safety evaluation. Subjects with non-interpretable dosimetry scans may be replaced upon agreement of the investigator and the sponsor.

For Cohorts 3 and 6 in Part B, to detect a difference between two peptide doses within the same cohort, the total sample size of eight is calculated. Assuming 30% standard deviation of the paired difference, there is 80% power to detect a 2-fold-change, and 99% power to detect a 3-fold change at a 2-sided alpha of 0.05.

2 SUBJECT ANALYSIS SETS

The following Analysis Sets will be used during statistical analyses

Screened Subjects Set, i.e. all subjects screened (i.e. who signed the informed consent)

Eligible Subjects Set, all subjects who comply with the inclusion and exclusion criteria (according to the investigator/site) and have entered the study (performed the Screening Visit).

2.1 Efficacy

2.1.1 Intent-To-Treat Set (ITT)

The Intent-to-Treat Set (ITT) consists of all subjects in the Eligible Subjects Set who received study medication.

2.1.2 Per Protocol Set (PP)

The Per-Protocol Set (PP) consists of all subjects in the ITT Set who complete the study according to the protocol with no major protocol deviation. Any protocol deviation will be evaluated by the Sponsor based on the individual case. Major protocol deviations will be defined in the Protocol Deviations Document and identified in a data review meeting before database lock.

2.2 Safety

The Safety Analysis Set (SAS) will consist of all subjects who received study medication.

2.3 Dosimetry

2.3.1 Intent-To-Treat Dosimetry Analysis Set (ITT-DAS)

The Intent-To-Treat Dosimetry Analysis Set (ITT-DAS) consists of all subjects in the ITT Set for whom at least one complete set of dosimetry imaging and dosimetry blood sample measurements is available.

2.3.2 Per Protocol Dosimetry Analysis Set (PP-DAS)

The Per Protocol Dosimetry Analysis Set (PP-DAS) will consist of all subjects in the ITT-DAS for whom no major protocol violations occurred affecting dosimetry variables.

2.4 Pharmacokinetics

2.4.1 Radiopharmaceutical Pharmacokinetic Set

For Part A and Part B, the Radiopharmaceutical Pharmacokinetic Set will consist of all subjects in the ITT Set who receive at least one dose of study medication and have at least one measured radioactive concentration in blood.

2.4.2 OPS201 Pharmacokinetic Set (Part B only)

For Part B only, the OPS201 Pharmacokinetic Set will consist of all patients in the ITT Set who receive at least one dose of study medication and have no major protocol deviations affecting the PK variables and who have a sufficient number of OPS201 levels to estimate the main PK parameters (i.e. C_{max}, T_{max}, and Area Under the Curve (AUC)).

2.4.2.1 OPS201 Pharmacokinetic Set in Plasma (Part B only)

For Part B only, the OPS201 Pharmacokinetic Set will consist of all patients in the ITT Set who receive at least one dose of study medication and have no major protocol deviations affecting the plasma PK variables and who have a sufficient number of plasma OPS201 levels to estimate the main PK parameters (i.e. C_{max}, T_{max}, and Area Under the Curve (AUC)).

2.4.2.2 OPS201 Pharmacokinetic Set in Urine (Part B only)

For Part B only, the OPS201 Pharmacokinetic Set will consist of all patients in the ITT Set who receive at least one dose of study medication and have no major protocol deviations affecting the urine PK variables and who have all urine OPS201 levels available to estimate the main urine PK parameters (i.e. Ae, f_e and Cl_R).

2.5 Primary Analysis Set

The primary analysis based on the assessment of the safety and tolerability of the study drug (primary objective) will be performed on the Safety Analysis Set (SAS).

The efficacy analysis will be performed on the ITT and PP sets.

Patients will be assigned to each analysis set prior to the statistical analysis.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [3] and will be based on the pooled data from the individual study sites, unless otherwise stated. Statistical analyses will be performed by Covance.

3.1.1 Primary safety endpoint(s)

Frequencies and/or descriptive summaries of standard safety and tolerability parameters: AEs (including SAEs) according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and vital signs, laboratory tests (haematology, biochemistry and urinalysis, and pituitary markers), 12-lead and Holter electrocardiogram (ECG), DLTs, physical examination results and use of concomitant medication throughout the study.

3.1.2 Secondary endpoint(s)

3.1.2.1 Biodistribution and Radioactive Pharmacokinetics of the Radiopharmaceutical Endpoints

Biodistribution and Pharmacokinetics (including radioactive decay) of the Radiopharmaceutical endpoints are:

(a) Maximal uptake (unit: %) in lesions.

The maximal uptake in lesions will be calculated for each lesion as:

$$\text{Maximal uptake (\%)} = \frac{Maximal\ activity\ (Bq)}{Injected\ activity\ (Bq)} \times 100$$

With:

Maximal activity (unit: Bq): the maximal activity in each eligible lesion, on all the assessment performed within each cycle (at Visits 1-3: 4 hours, 24 hours, 48 hours, 72-96 hours, and 144-168 hours post infusion).

Injected radioactivity (IA) (unit: Bq): the actual radioactivity administered/injected.

Maximal uptake (%) in lesions will be computed for each administration of ^{177}Lu-OPS201 (visits 1, 2, 3, 4 and 5). Uptake (%) at each time point will be also calculated and displayed for the statistical analysis.

(b) Maximal uptake (unit: %) in discernible organs.

The maximal uptake in discernible organs will be calculated with the same formula as for the lesions.

Discernible organs will be identified during the course of the study.

Maximal uptake (%) in discernible organs will be computed for each administration of ^{177}Lu-OPS201 (visits 1, 2, 3, 4 and 5). Uptake (%) at each time point will be also calculated and displayed for the statistical analysis.

(c) Area Under the Curve (AUC) of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs (unit: MBq*h), lesions (unit: MBq*h) and blood (unit: MBq/L*h).

The AUCs of ^{177}Lu-OPS201 will be computed through sum of exponential functions fitting and integration (Ref. 11) as decribed in the Dosimetry Calculation Procedure Manual.

AUC of ^{177}Lu-OPS201 radioactivity in discernible thoracic and abdominal organs, lesions and blood will be computed for each administration of ^{177}Lu-OPS201.

Radioactivity uptake in blood in percentage of the IA per liter (unit: %/L) at each assessment time point will be also displayed (i.e. at Visit 1: before infusion, at stop of infusion (0), 5 minutes ± 1 minute, 30 minutes ± 3 minutes, 1 hour ± 5 minutes, 4 hours ± 10 minutes, 24 ± 1 hours, 48 ± 1 hours and 72-96 hours and 144-168 hours after the stop of infusion, Visits 2, 3, 4 and 5: before infusion, at stop of infusion (0), 1 hour ± 5 minutes, 4 hours ± 10 minutes, 24 ± 1 hour, 48 ± 1 hour, 72-96 hours and 144-168 hours).

(d) Terminal half-life of radioactivity concentrations in blood (unit: h).

The terminal half-life is defined as the lowest decay rate of the AUC fit performed for blood (Ref. 11).

(e) Other biodistribution and radioactive pharmacokinetics of the radiopharmaceutical variables

Cumulatively excreted activity in urine (unit: MBq) in each time period, 0 to 6 hours and 6 to 24 hours post-infusion (Part A), and 0 to 4 hours, 4 to 24 hours, 24 to 48 hours (Part B).

3.1.3 Radiation dosimetry endpoint(s)

Radiation dosimetry endpoints are the following (calculations methods are described in the Dosimetry Calculation Procedure Manual):

(a) Absorbed dose in organs/ lesion (unit: Gy).

(b) Specific absorbed dose to the lesions (unit: Gy/GBq)

The specific absorbed dose to the lesions is the absorbed dose by the lesion (unit: Gy) divided by the injected radioactivity (unit: GBq) for each lesion selected for dosimetry evaluation.

Specific absorbed dose to the lesions (unit: Gy/GBq) will be computed for each administration of ^{177}Lu-OPS201 (visits 1, 2 and 3) on part A, and on Part B (Cohort 1, 3 and 6), for each lesion lesion evaluable in dosimetry (all lesion and by lesion location) when at least 3 patients in the same cohort is having a lesion in the same organ, by visit and overall.

(c) Specific absorbed dose per organ (unit: Gy/GBq).

The specific absorbed dose for a given organ is the absorbed dose by this organ (unit: Gy) divided by the injected radioactivity (unit: GBq).

Specific absorbed dose per organ (unit: Gy/GBq) will be computed for each administration of ^{177}Lu-OPS201 (visits 1, 2 and 3) and any additional cycle.

(d) Cumulative absorbed doses in organs and lesions selected for dosimetry evaluation (unit: Gy).

The cumulative absorbed organ dose is calculated as the sum of the absorbed dose over all the ^{177}Lu-OPS201 administration cycles. In case absorbed dose is missing for at least one of the ^{177}Lu-OPS201 administration cycles, cumulative absorbed dose is extrapolated from available data at the other cycles by dosimetry expert.

Cumulative absorbed doses will be provided per organ and for lesions selected for dosimetry evaluation.

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[redacted]

3.1.5 OPS201 Pharmacokinetics (Part B only)

In subjects in plasma OPS201 PK Set, plasma PK parameters of OPS201 (including, but not limited to, maximum observed concentration (C_{max}), AUC, elimination half-life ($t_{1/2}$), apparent total body clearance of the drug from plasma (CL), apparent volume of distribution (Vd)) will be derived using the non-compartmental approach on the individual plasma concentration-time profiles of OPS201.

In subjects in urine OPS201 PK Set, urine PK parameters of OPS201 (including, but not limited to, cumulative amount of unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma (CLR)) will be derived using the non-compartmental approach.

Derivation and analysis of PK data will be documented in a separate Data Analysis Plan.

3.1.6 Secondary Efficacy Endpoints

The efficacy endpoints are:

(a) Objective tumour response based on RECIST v1.1 (CT/MRI scan)

- Best overall response (BOR)

The best overall response according to RECIST v1.1 is defined as the best response recorded from the initiation of treatment until the EOCT/ EOAC/EW Visit, prior to the assessment of PD. Confirmation of complete or partial response is not required.

The following table provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline:

Table 4 Time point response

Target Lesions	Non-Target Lesions	New Lesions[a]	Time Point Response (TPR)
CR	CR	No	CR
CR	NCRNPD	No	PR
CR	NE	No	PR[b]
CR	NA[c]	No	CR
PR	NE	No	PR[b]
PR	CR	No	PR
PR	NCRNPD	No	PR
PR	NA[c]	No	PR
SD	NE	No	SD
SD	CR	No	SD
SD	NCRNPD	No	SD
SD	NA[c]	No	SD
NE	Non-PD	No	NE
PD	ANY	Yes/No	PD
ANY	PD	Yes/No	PD
ANY	ANY	Yes	PD

CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, NE: Not Evaluable, NCRNPD: Non-CR/Non-PD, NA: Not Applicable.

a Identification of new lesions at a post-Screening time point will result in a TPR of PD. If an identified new lesion subsequently becomes NE, the TPR will be recorded as PD unless the new lesion has proven to have resolved. Note: TPRs assessed after a progression event will not contribute to the determination of the Best Response.

b If a non-target lesion is classified as NE, a designation of PR may be assigned based on information from the target lesions.

c No non-target lesions identified at Screening.

When SD or Non CR/Non Progressive Disease is believed to be the best overall response, it needs to be assessed a minimum of 8 weeks [56 days] after start of treatment. Otherwise, the best overall response will be NE, unless any Progressive Disease was further documented, in which case BOR will be Progressive Disease.

- Overall Response Rate (ORR)

The Overall Response Rate (ORR) is defined as the proportion of participants who achieved a Complete Response (CR) or a Partial Response (PR) as best overall response according to RECIST v1.1 criteria in the ITT Set. Subjects with no tumour assessment after the start of study treatment will not be evaluated.

- Disease Control Rate (DCR)

The DCR is defined as the proportion of participants who achieved a Complete Response (CR), a Partial Response (PR) or a Stable Disease (SD) as best overall response according to RECIST v1.1 criteria in the ITT Set. Subjects with no tumour assessment after the start of study treatment will be considered as with no disease control.

- Sum of diameters as percentage change
  - Percentage change from baseline in the target lesions identified in the RECIST v1.1 assessment and/or the initial lesion(s) identified at eligibility as being >20 mm in diameter, calculated as:

Percentage change from baseline $= \frac{(Di-D0)}{D0} \times 100$

With

Di the sum of the longest diameters of the target lesions as per RECIST v1.1 at the time point/Visit *i*.

D0 the sum of the longest diameters of the target lesions as per RECIST v1.1 at baseline.

  - Best percentage change from baseline in sum of target lesions longest diameters, calculated as:

Best percentage change from baseline $= \frac{(Dmin-D0)}{D0} \times 100$

With:

Dmin the minimum sum of the longest diameters as per RECIST v1.1 on all measurement time points.

D0 the sum of the longest diameters of the target lesions as per RECIST v1.1 at baseline.

Correlations will be computed between dosimetry parameters (cumulative absorbed dose) and volume and diameter changes in lesions at the last visit of the core trial (EOCT or EACT or EW as applicable).

(b) Progression Free Survival (PFS)

PFS will be evaluated up to two years after the EOCT/EOAC Visit and will be based on RECIST v1.1 status assessed by investigator assessment. PFS will be assessed by independent central review up to EOCT/ EOAC/EW Visit (during the core study part).

PFS is defined as the time from start of study treatment until occurrence of tumour progression or death.

(c) Quality of life using EORTC QLQ C30 v3.0 and QLQ GI.NET21 (2006) questionnaires.

- EORTC QLQ C30 v3.0

The European Organisation for Research and Treatment of Cancer (EORTC) score questionnaire (QLQ-C30) will be used for quality of life (QoL) evaluation.

Following the EORTC recommendations, fifteen scales can be derived from the initial 30 questions:

- A global health status/QoL scale,
- Five functional scales (physical, role, cognitive, emotional and social),
- Nine "symptoms" scales /items (nausea and vomiting, pain, fatigue, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).

Of note, for functional scales, a higher value reflects a better level of function, but for symptoms scales /items a higher value reflects worse symptoms; moreover high score for the global health status represents a high QoL.

Each scale in the questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method is summarized below. In this summary, Qi refers to the ith question on the EORTC QLQ-C30.

Table 5 Scoring and scale dimension for EORTC QLQ-C30:

	Number of items (range[a])	**Item number**
Global health status / QoL		
Global health status/QoL	2 (6)	29,30
Functional scales		
Physical functioning	5 (3)	1 to 5
Role functioning	2 (3)	6, 7
Emotional functioning	4 (3)	21 to 24
Cognitive functioning	2 (3)	20, 25
Social functioning	2 (3)	26, 27
Symptom scales / items		
Fatigue	3 (3)	10, 12, 18
Nausea and vomiting	2 (3)	14, 15
Pain	2 (3)	9, 19
Dyspnoea	1 (3)	8
Insomnia	1 (3)	11
Appetite loss	1 (3)	13
Constipation	1 (3)	16
Diarrhoea	1 (3)	17
Financial difficulties	1 (3)	28

[a] Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

For all scales, the RawScore, RS, is the mean of the component items:

RawScore RS = $(I_1 + I_2 + ... + I_n)/n$

Then **for Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales** / **items** and **Global health status** / **QoL**:

$$Score = \left\{\frac{(RS - 1)}{range}\right\} \times 100$$

Missing value (item) consideration for scoring:

The scale scores will only be calculated if at least half of the items from the scale have been answered. Otherwise, no score will be calculated, and the scale score will be set to missing.

For single-item measures, the score will be missing if the question is not answered.

- EORTC QLQ – GI.NET21 (2006)

The GI.NET21 module is intended for use among subjects with gastrointestinal related (GI.-related) neuroendocrine tumours, who vary in disease stage and treatments.

The module comprises 21 questions, consisting of 5 scales and 4 single items, assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality. The module has been developed according to the EORTC guidelines. The GI.NET21 has been translated into several European languages.

Each question is quoted from 1 (Not at all) to 4 (very much). The scoring algorithm for the scales and single items is described below:

Table 6 Scoring and scale dimension EORTC QLQ – GI.NET21:

	Number of items (range[a])	**Item number**
Scales		
Endocrine symptoms scale	3 (3)	31, 32, 33
G.I. symptoms scale	5 (3)	34 to 38
Treatment related symptom scale	3 (3)	39, 40, 46
Social function scale	3 (3)	42, 44, 49
Disease related worries scale	3 (3)	41, 43, 47
Single items		
Muscle /bone pain symptom	1 (3)	48
Sexual function	1 (3)	51
Information/communication function	1 (3)	50
Body Image	1 (3)	45

[a] Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

For all scales, a high score is equivalent to worse or more problems.

For all scales, the RawScore, RS, is the mean of the component items:

$$RawScore\ RS = (I_1 + I_2 + ... + I_n)/n$$

Then for each of the five **scales** and for each **single item**:

$$\text{Score} = \left\{\frac{(RS-1)}{range}\right\} \times 100$$

Missing value (item) considerations for scoring are the same as for the QLQ-C30 questionnaire presented above.

3.1.7 Exploratory endpoint(s)

3.1.7.1 Exploratory Efficacy Endpoints

CCI

[redacted]

CCI

[redacted]

3.1.7.2 Exploratory Biomarkers

CCI

[redacted]

3.1.8 Multiplicity

No multiple testing will be performed in this study.

3.1.9 Significance testing and estimation

As this is a descriptive safety and tolerability/efficacy study, no formal statistical testing will be carried out. If p-values are provided, they will only be provided for exploratory purposes only.

3.2 Analysis methods

3.2.1 Safety

All safety data will be included in the data listings and summary tables will be based on the Safety Analysis Set. Summary tables will be presented by study Part, cohort (part B only), overall Part B and overall.

3.2.1.1 Dose Limiting Toxicity

DLTs (see section 3.2.18) will be listed by study Part, cohort (part B only), radioactivity level adapted or not (part B only) and subject. Listings of AEs and abnormal laboratory values defined as DLTs will be also provided sorted by study Part, cohort (part B only), radioactivity level adapted or not (part B only) and subject.

A summary of DLTs will be provided, presenting the number of subjects with DLTs, the number of DLTs and the number of DTLs per type of DLTs (presented by decreasing frequency), by study Part, cohort (part B only), radioactivity level adapted or not (part B only) and overall.

3.2.1.2 Adverse events

All AEs will be recorded and graded by investigators using the NCI CTCAE classification v5.0 and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1 or higher and will be classified by MedDRA preferred term and system organ class.

Listings will be presented and sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject number, start time of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study.

Listings of all adverse events, serious adverse events (SAE), adverse events leading to withdrawal, adverse events leading to dose reduction, adverse events leading to dose interruption, adverse events leading to dose delayed, adverse events with CTCAE Grade 3,4 and 5 and listings of deaths will also be presented.

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

A TEAE is defined as any adverse event that occurs up to 6 months (180 days) post last dose if:

(1) it was not present prior to receiving the first dose of IRPP (or OPS301 if applicable), taking into account the time of administration and the time of AE, or

(2) it was present prior to receiving the first dose of IRPP (or OPS301 if applicable) but the intensity/grade increased during the active phase of the study, taking into account the time of administration and the time of AE, or

(3) it was present prior to receiving the first dose of IRPP (or OPS301 if applicable), the intensity/grade is the same but the causality changed to “related” during the active phase of the study, taking into account the time of administration and the time of AE.

Phase of the study will be defined into 3 time periods:

- period 1: treatment intake up to 56 days/8 weeks (corresponding to 8 half-lives of the ^{177}Lutetium rounded to the upper number of weeks, 162 hours * 8 + 2 days) after last dose
- period 2: 57 days up to 6 months post last dose
- period 3: after 6 months of last dose until 2-year follow-up period /death or lost to follow-up

An overall summary table (by period 1, 2 and 1+2) of all treatment emergent adverse events will be presented by study part, cohort (part B only) and overall using the Safety Analysis Set. This table will be also repeated for period 3.

All AEs and SAEs occurring during the Screening period and more than 6 months after the last dose of study medication will be listed and flagged as occurring before or after (during period 3) the active phase of the study; however, these will not be defined as TEAEs.

TEAEs will be summarised by study part, cohort (part B only) and overall with the number and percentage of subjects with adverse events classified by primary system organ class and preferred term. The number of occurrences of a TEAE will also be presented. The summary of AEs will also be repeated by time period. A listing of AEs by time period will also be presented.

In addition, summary tables will also be presented for SAEs, TEAEs related to ^{177}Lu-OPS201, TEAEs related to OPS301, treatment emergent ^{177}Lu-OPS201 related SAEs, OPS301 related SAEs, TEAEs leading to premature discontinuation of study medication, TEAEs leading to dose delays, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs per decreasing frequency, TEAEs by associated NCI CTC worst grade and by causality. There will also be a separate summary for Adverse Events of Special Interest (AESI) which will be defined as any TEAE related to ^{177}Lu-OPS201 which occurs the day of ^{177}Lu-OPS201 administration (same date as ^{177}Lu-OPS201 administration and at any cycle).

Summary tables of adverse events will be provided with the number and percentage of subjects with adverse events classified by primary system organ class, preferred term (ordered alphabetically) and associated CTCAE version 5.0 worst grade. In the event of multiple occurrences of the same adverse events 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> not related) will be chosen.

3.2.1.3 Laboratory data

A separate listing of normal ranges for SI and local laboratories units will be provided by study site laboratory, gender and age where relevant.

Laboratory data (including hematology, biochemistry, pituitary markers and urinalysis) will be listed in SI and local laboratories units and abnormal values will be flagged (High, [H], Low [L], clinically significant [C], CTCAE version 5.0 grade (G)) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings. In addition, a listing of clinically significant abnormal values will be presented.

As multiple local laboratories are used within the study, a data normalisation method (refer to Appendix 1: Derived Data, and Ref. 5, 6, 7) will be used before summarising the data. The normalized lab data values will be also included in the lab data listings together with the reference normal range limits used for the normalisation.

(a) Hematology, Biochemistry and Pituitary Markers

For hematology, biochemistry and pituitary marker parameters, the baseline will be defined as the last measurement collected prior to the first dose of study drug.

For hematology, biochemistry and pituitary marker parameters, summary statistics, by study part, cohort (part B only) and overall, will be presented at each scheduled assessment for normalised actual values and changes from baseline. For pituitary markers, all values will be displayed in a listing, however the summary tables may exclude any results if it was drawn while the subject was receiving medication that may have been deemed to impact the result.

The determination of the medications impacting the result will be based upon medical monitor review and reflected in a footnote.

Shift tables from Baseline to worst post-baseline and also, each post baseline visit. In the shift tables, the number and percentages of subjects with low, normal, or high values will be presented by study part, cohort (part B only) and overall.

For hematology and biochemistry, summary statistics by study part, cohort (part B only) and overall, will be also provided for nadir and day to nadir by cycle (time from cycle baseline to nadir during the same cycle) and on lab toxicities after start of study medication with worst CTCAE version 5.0 Grades 3 and 4 (refer to Appendix 1, Derived data).

Shift tables from Baseline to worst CTCAE version 5.0 Grade of hemoglobin, absolute neutrophil count, and platelet count, will be presented by study part, cohort (part B only) and overall.

Hematological and biochemistry toxicities will be recorded and graded according to the CTCAE criteria, Version 5.0. The CTCAE grade (0 to 4) of hematology and biochemistry by cycle and by subject will be listed in the Section 16.2.8. Listings of the laboratory parameters in section 14.3.4 will include a listing of all CTCAE Grade 3 and 4 hematological toxicities, a listing of CTCAE Grade 3 and 4 hematological toxicities lasting 4 weeks or more, a listing of CTCAE Grade 2 hematological toxicities lasting 4 weeks or more, a listing of all CTCAE Grade 3 and 4 biochemical toxicities, a listing of CTCAE Grade 3 and 4 biochemical toxicities lasting 4 weeks or more, a listing of CTCAE Grade 2 biochemical toxicities lasting 4 weeks or more, a listing of all eGFR of < 45mL/min, a listing of eGFR of < 45mL/min lasting 4 weeks or more, a listing of out of range biochemistry parameters that could not be graded using CTCAE grade (below LLN – normal – above ULN) and a listing of biochemistry parameters that could not be graded using CTCAE grade (below LLN – normal – above ULN) lasting 4 weeks or more.

In addition, figures of absolute leucocyte count, absolute neutrophil count, absolute lymphocyte count, platelet count, hemoglobin, AST, ALT, AP, total bilirubin, creatinine, eGFR individual normalised values over time will be displayed.

(b) Urinalysis

For categorical urinalysis data (absent/trace/positive and normal/abnormal) frequency tables, by study part, cohort (part B only) and overall, will be presented at each scheduled assessment as well as the change from baseline with the following categories: improved, stable, worsened and abnormal worsening.

Shift tables from Baseline to each post baseline visit for the number and percentage of subjects with normal, abnormal clinical evaluation will be presented by study part, cohort (part B only) and overall.

For continuous urinalysis data (specific gravity, PH), summary statistics, by study part, cohort (part B only) and overall, will be presented at each scheduled assessment for actual values and changes from baseline.

3.2.1.4 Vital signs, weight and height

Vital signs (supine blood pressure, supine heart rate, body temperature, body weight, BMI and BSA) will be listed at each assessment by study part, cohort (part B only), radioactivity level adapted or not (part B only) and subject. Any unscheduled vital signs assessment will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug.

Summary statistics (n, mean, standard deviation, median, minimum and maximum) for supine blood pressure, supine heart rate, body weight, BMI and BSA by study part, cohort (part B only) and overall, will be presented at each scheduled assessment for actual values and changes from baseline.

3.2.1.5 ECG

Descriptive summaries of the following ECG and Holter parameters will be calculated: heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB, and QTcF. The number and percentage of subjects with normal, abnormal (not clinically significant), abnormal (clinically significant) findings will be presented for patients in the Safety Analysis Set.

3.2.1.6 Physical Examination

Physical examination results (Normal / Abnormal) will be listed at each assessment by study part, cohort (part B only), radioactivity level adapted or not (part B only) and subject. Any unscheduled physical examination will be flagged [U] in the listings.

3.2.1.7 Extent of Exposure

The extent of study treatment exposure will be summarized by cohort, part and overall within the safety population.

The overall study treatment exposure will be summarized by:

- the number of cycles,
- actual cumulative dose defined as the sum of all doses of 177luOPS201 from the first dose to the last one. If one administered radioactivity dose is missing, the cumulative dose will not be calculated and will be set to missing.
- actual cumulative dose by cycle defined as the sum of all doses taken until the cycle presented. If one administered radioactivity dose is missing, the cumulative dose will not be calculated and will be set to missing
- duration of exposure (defined in section 7.1)
- overall study duration (defined in section 7.1)
- number of patients with OPS301 at any cycles

3.2.1.8 Performance status (Karnofsky scoring)

The performance status of the subjects as defined by the Karnofsky scoring:

- 100 - Normal; no complaints; no evidence of disease.
- 90 - Able to carry on normal activity; minor signs or symptoms of disease.

- 80 - Normal activity with effort; some signs or symptoms of disease.
- 70 - Cares for self; unable to carry on normal activity or to do active work.
- 60 - Requires occasional assistance, but is able to care for most of his personal needs.
- 50 - Requires considerable assistance and frequent medical care.
- 40 - Disabled; requires special care and assistance.
- 30 - Severely disabled; hospital admission is indicated although death not imminent.
- 20 - Very sick; hospital admission necessary; active supportive treatment necessary.
- 10 - Moribund; fatal processes progressing rapidly.
- 0 – Dead

Karnofsky performance status score will be analysed as quantitative variable and qualitative variable.

For Karnofsky performance status score as quantitative variable, descriptive statistics and 95% Confidence Interval (CI) of the mean will be presented for the raw data and for the changes from baseline during treatment, by study part, cohort (part B only) and overall at each visit (Visit 1, 2, 3 and EOCT Visit).

For Karnofsky performance status score as qualitative variable (class), the number and percentage of subjects per score level and per level of change from baseline, summarized as Worsening, No change and Improvement, will be provided by study part, cohort (part B only) and overall at each visit (Visit 1, 2, 3 and EOCT Visit). The shift from baseline at each visit will be also provided.

3.2.2 Radiopharmaceutics and Dosimetry

All data will be included in the individual data listings and summary tables will be based on the PP-DAS, Radiopharmaceutical Pharmacokinetic Set or ITT-DAS Set depending of the parameter. Summary tables will be presented by study part, cohort (part B only), overall part B and overall.

(a) Biodistribution and Radioactive Pharmacokinetics

- Maximal uptake (unit: %) in lesions.

Maximal uptake (unit: %) in lesions will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and lesion number. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only) and cycle on the PP-DAS.

Uptake (unit: %) in lesions at each assessment time point will be also displayed, it will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle, lesion number and time point.

- Maximal uptake (unit: %) in discernible organs.

Maximal uptake (unit: %) in discernible organs will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and organ. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only) and cycle on the PP-DAS.

Uptake (unit: %) in discernible organs at each assessment time point will be also displayed, it will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle, organ and time point, along with dosimetry parameters. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and time point on the PP-DAS. A linear plot of the mean of the uptake (%) in discernible organs over time will be displayed by study part, cohort (part B only), radioactivity level adapted or not (part B only) and cycle on PP-DAS.

- Areas Under the Curve (AUCs) of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs (unit: MBq*h), lesions (unit: MBq*h) and blood (unit: MBq/L*h).

AUCs of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs (unit: h*MBq) will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only) , subject, cycle and organ. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle, organ on the PP-DAS.

AUCs of ^{177}Lu-OPS201 in lesions (unit: h*MBq) will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only) , subject, cycle and lesion number.

AUCs of ^{177}Lu-OPS201 in blood (unit: MBq/L*h) will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject and cycle. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only) and cycle on the Radiopharmaceutical Pharmacokinetic Set.

- Uptake in blood (unit: %/L)

At each assessment time point will also displayed, it will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and time point. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and time point on the Radiopharmaceutical Pharmacokinetic Set. Graphs of the mean of the uptake in blood (unit: %/L) over time will be displayed by study part, cohort (part B only), radioactivity level adapted or not (part B only) and cycle on the Radiopharmaceutical Pharmacokinetic Set.

- Terminal half-life of radioactivity concentrations of the radiopharmaceutical in blood (unit: h).

Terminal half-life of radioactivity concentrations in blood (unit: h) will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject and cycle. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), radioactivity level adapted or not (part B only) and cycle on the Radiopharmaceutical Pharmacokinetic Set.

- Cumulatively excreted radioactivity in urine (unit: MBq) in each time period, 0 - 6 hours, 6 - 24 hours and 24 - 48 hours and overall on the 0-48 hours period (if there is no missing collection period).

Cumulatively excreted radioactivity in urine (unit: MBq) will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and time period.

Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and time period on the ITT Set.

(b) Radiation Dosimetry

- Organs receiving the highest absorbed dose (unit: Gy).

All organs with their absorbed dose will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), cycle, organ and subject on the ITT- DAS, and highest dose will be flagged.

- Specific absorbed dose to the lesions selected for the dosimetry evaluation (unit: Gy/GBq).

Specific absorbed dose to the lesions selected for the dosimetry evaluation will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and lesion number. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and lesion location on the ITT- DAS and PP-DAS. Descriptive statistics will also be presented on combined lesions on the PP-DAS population.

- Specific absorbed dose per organ (unit: Gy/GBq).

Specific absorbed dose per organ will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, cycle and organ. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and organ on the ITT- DAS and PP-DAS.

- Ratio of Specific absorbed dose per organ and lesion.

Ratio of specific absorbed dose at visits (e.g. visit 2 relative to visit 1, visit 3 relative to visit 1, visit 2 relative to visit 3, etc..) will be calculated per organ and per lesion and by study part (Part A and B), and by each cohort (applies to part B only), radioactivity level adapted or not (applies to part B only), subject, cycle and organ. Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and organ on the PP-DAS.

Boxplots representing the ratio of specific absorbed doses between visits by organ and lesion will be produced.

- Tumour average/kidney ratio

Ratio of tumour/average kidney ratio between visits by organ or combined lesions will be calculated per lesion and by study part (Part A and B), and by each cohort (applies to part B only), radioactivity level adapted or not (applies to part B only), subject and cycle.

Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only), cycle and organ on the PP-DAS.

- Cumulative absorbed organ doses (unit: Gy)

Cumulative absorbed organ doses will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only), organ and subject.

Descriptive statistics, including geometric mean and geometric Coefficient of Variation (CV), will be presented by study part, cohort (part B only) and organ on the ITT- DAS and PP-DAS.

CCI

(d) OPS201 Pharmacokinetics (Part B only)

Analysis of PK data by non-compartmental approach will be documented in a separate analysis plan. A listing of PK sampling time deviation from the scheduled time will be provided on OPS201 PK population. A listing of individual OPS201 concentrations per time point will be provided on OPS201 PK population.

3.2.3 Efficacy

All efficacy data will be included in the data listings and summary tables based on the ITT and PP sets. Summary tables will be presented by study part, cohort (part B only), overall part B and overall.

Tumour response will be evaluated by an independent central review and by the site investigator.. Response and progression will be evaluated using the revised RECIST guideline v1.1 and a modified RECIST (will be analysed for both Part A and B. The efficacy endpoint in the protocol only focus on Part B patients) guideline. Only subjects with measurable disease at baseline, who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

Investigator assessment using RECISIT (V1.1) will be the primary assessment whereas central RECIST (V1.1) and mRECISIT (part B only) will be sensitivity analysis.

a) Overall Response, Best Overall Response and Overall Response Rate

Overall response at each visit will be tabulated and listed, as well as Best Overall response according to RECIST/CCI. Subjects with concurrent use of somatostatin analogues will be flagged in the listing.

For analysis of the ORR, summary tables will be generated, presenting the number and proportion of responders by study part, cohort (part B only) and overall on the ITT and PP sets, together with two-sided 95% Clopper-Pearson CIs. Subjects with no tumour assessment after the start of study treatment will be excluded from the analysis.

The same analysis might be repeated in the subsets of subjects with and without concurrent use of somatostatin analogues, if deemed relevant by the Sponsor.

The following SAS® code will be used for tables that need exact 95% Clopper-Pearson CIs:

```
PROC FREQ DATA=dset NOPRINT;
        BY by var; (optional)
        TABLES var1 /binomial (exact);
        OUTPUT OUT=outname;
RUN;
```

b) Disease control rate (DCR)

The number and proportion of subjects with disease control at end of either EOCT/EOAC (if independent central read) or end of long-term follow-up (if investigator) will be presented per study part, cohort (part B only) and overall on the ITT and PP sets, together with two-sided 95% Clopper-Pearson CIs. Subjects with no tumour assessment after the start of study treatment will be excluded from the analysis. The DCR will be based on the best overall response over all timepoints for independent central review and investigator assessment.

For investigator data, the DCR rate at selected timepoints (Month 12, 18, 24) will also be generated. For DCR at month 12 (resp. 18 and 24 month), the analysis will include all patients who are on study at month 12 (resp. 18 and 24 month) defined as 365 days – 28 days (resp. 545 - 28 and 730- 28) relative to the first dose or patients who had early PD or death prior to that time. The best overall response category of CR, PR or SD in patients who have not had an early PD or death up to the timepoint will represent the subjects with disease control

c) Sum of Diameters

Descriptive statistics and 95% CIs of the mean for percentage change from baseline will be calculated by study part, cohort (part B only) and overall at Follow-up Visit 2, EOCT, EOAC (if any) and Long-Term Follow-up visits on the ITT and PP sets. The length of the longest diameter will also be presented.

Percent change and best percent change in sum of diameters will be listed.

Percent change of sum of diameters according to RECIST[CCI] will also be plotted by study part and cohort (part B only) at Visit 2, EOCT Visit, EOAC Visit (if any) and Long-Term follow up visits 1 and 2 on the ITT set.

Waterfall plots presenting best overall response (RECIST[CCI]) versus best percent change from baseline of sum of target lesion diameters over the whole study will be performed on the ITT set.

d) Progression Free Survival (PFS) from independent central review and from investigator assessment

PFS, defined as the time from first study drug administration to progression or death which ever occur first, will be analysed.

Disease progression will be assessed by tumour response evaluation according to RECIST v1.1/[CCI], measured using the same imaging technique (ceCT scan or MRI) for each subject throughout the study.

Event dates are assigned to:

- The first time when progressive disease was noted, or
- Date of death.

In case of progressive disease followed by death, the first event will be considered in the analysis. The date of progression will be recorded as the date of the last radiographic evaluation included in the series for that assessment.

Censoring dates are defined in subjects with no progressive disease or death before end of study or withdrawal. In these subjects, the censoring date is defined as the last date on which overall

RECIST status was evaluable. This is taken to be the date of the last radiological assessment at which the target lesions were evaluated (see Table 7).

Table 7 Censoring Rules for PFS

Reason for censoring	Rule
No screening evaluable[a] assessment	Date of first treatment administration
Two or more not evaluable (NE) consecutive assessments before progressive disease or death	Date of last evaluable disease assessment before the second NE assessment
No progressive disease	Date of last evaluable disease assessment
Treatment discontinuation for undocumented progression	Date of last evaluable disease assessment
Treatment discontinuation for toxicity or other reason	Date of last evaluable disease assessment
Initiation of medications or therapy not permitted during the study	Date of initiation of non-permitted medication or therapy

a An assessment is considered NE when no imaging/measurement is done at all at a particular time point, or only a subset of lesion measurements are made at the time point. The subject is considered NE at that time point.

For central reading assesments, patients will be censored at the timepoint of the last central assessment at or before EOCT/EOAC.

The PFS time will be calculated as the time from first administration of the study drug to either progressive disease or death as follows.

PFS time (in months) = [(Date of event – date of first administration of study drug + 1] / 30.4375

Data will be analysed by study part, cohort (part B only) and overall part B on the ITT and PP sets. The distribution of PFS times will be estimated using the Kaplan Meier method for each study part, cohort (part B only) and overall Part B. The median PFS time will be presented with its associated 95% CI, together with the number and percentage of events, by study part, cohort (part B only) and overall. The results will also be presented graphically in Kaplan Meier plots.

Completely missing tumour data: when tumour assessment visits are completely missing, FDA Guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” [4] states that "events occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate assessment”.

This will be implemented as follows:

Progressive Diseases (PDs) occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate* assessment before the missing assessments: If a subject has one missed radiological assessment before a PD, the PD will be analysed as an event (i.e. a PD is analysed as an event if the previous radiological assessment was performed within approximately the last 6 months).

Table 8 Event status for various scenarios with missing data

Scan Time	FU Visit 2	EOCT/EOAC / EW Visit	Long-term Follow-up Visits n	Long-term Follow-up Visits n +1	Event status
Scenario 1	missing	PD			Event at EOCT/EOAC/EW visit
Scenario 2	missing	missing	PD		Censored at Baseline
Scenario 3	missing	SD	PD		Event at Long-term Follow-up Visit n
Scenario 4	missing	missing	SD	PD	Event at Long-term Follow-up Visit n+1
Scenario 5	SD	SD	missing	PD	Event at Long-term Follow-up Visit n+1
Scenario 6	SD	missing	missing	PD	Censored at FU Visit 2

e) Dosing and dosimetry in conjunction with tumour burden

A figure depicting the following relationship displaying the Pearson's correlation coefficient (and the associated 95% confidence interval):

- CCI
-

f) Quality of life

- EORTC QLQ C30 v3.0

For QLQ C30 global health status score, functional scales scores and symptom scales scores, descriptive statistics and 95% CIs of the mean will be presented for the raw data and for the changes from baseline during treatment, by study part, cohort (part B only) and overall at each visit (Visit 1, 2, 3, optional visits (if any) and EOCT/EOAC Visits) on the ITT and PP sets.

For the evaluation of the QLQ C30 scores values at baseline the EORTC QLQ C30 Reference Values manual (Ref. 12) or a more up to date reference will be used.

- EORTC QLQ – GI.NET21 (2006)

For GI.NET21 endocrine symptoms scale score, G.I. symptoms scale score, treatment related symptom scale score, social function scale score, disease related worries scale score, muscle /bone pain symptom item, sexual function item, information/communication function item and body Image item, descriptive statistics and 95% CIs of the mean will be presented for the raw data and for the changes from baseline during treatment, by study part, cohort (part B only) and overall at each visit (Visit 1, 2, 3 and EOCT Visit) on the ITT and PP sets.

g) Duration of Response (DoR)

DoR refers to the time when complete response (CR) or partial response (PR) is first observed until the time of progressed disease (PD) or death for the subjects whose best overall response is complete response (CR) or partial response (PR). If the subject did not have an event of PD or death, then DoR will be the time of last tumor assessment.

DoR will be listed.

Summaries of DoR will include summary statistics of duration, the number and the associated percentage of patients whose DOR is >3, >6, >9 and >12 months for Part A and Part B and overall (Part A and B). In case of sufficient responders, the median of DOR (calculated based on Kaplan-Meier) and 95% confidence interval of median time will also be summarized.

h) Tumour Volume (mL)

Tumour Volume (mL) is measured for each lesion at each scheduled visit by independent central review using RECIST (v1.1) and CCI. The sum of the tumour volume (mL) per visit will be computed and descriptive statistics of tumour volume, change in tumour volume and percentage change in tumour volume will be generated at each scheduled visit on the ITT and PP sets.

3.2.4 Missing data and outliers

3.2.4.1 Missing data

a) Efficacy endpoints

When tumour assessment visits are completely missing, rules from FDA Guidance "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" [4] will be implemented as described in section 3.2.3.

Any missing QoL data (EORTC QLQ C30 and QLQ GI.NET21 questionnaires) will be handled as described in section 3.2.3.

b) Safety endpoints

If a value required a retest (for laboratory values, vital signs), the closest non-missing value to the scheduled visit will be used in the summary tables.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries. This decision will be made during the Data Review Meeting and documented.

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

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

c) Blood/plasma/serum data

Any embedded BLQ value (i.e. single BLQ value occurring between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

In a single-dose setting, the BLQ data must be substituted by 0 for concentrations measured before the first quantifiable concentration.

In multiple-dose setting, all BLQ must be set as missing in the dataset.

BLQ values substituted by 0 are included in the PK/NCA calculation whereas missing values are ignored.

In any case, when all concentrations from a concentration-time profile are BLQ, they must be substituted by 0 and included in the PK analysis dataset.

3.2.4.2 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:

For partially missing dates for efficacy endpoints derived using tumour assessments, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before the first study drug administration, then the date of start of study treatment 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 part (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 this is 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 dose will be "≥2", similarly the duration of ongoing AEs or medication will be"≥xx" according to the start and last visit dates).

3.2.4.3 Outliers

Any outlier identified prior to database lock which is impossible/implausible will be excluded from the analysis. 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.

The decision of how to handle these outliers will be made during the Data Review Meeting and documented.

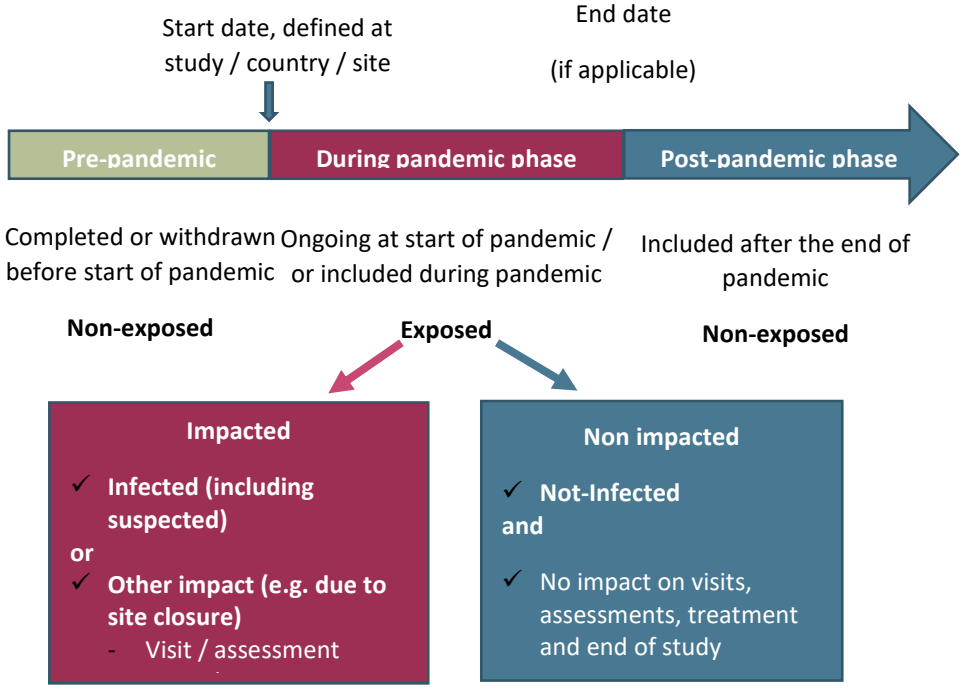
3.2.5 Subject disposition

A listing of dates of assessments (relative day), including EOCT, EOAC (part B only) and End of Long-term Follow-up (EOLTFU) dates and their study exposure will be presented by subject for each study part, cohort (part B only) and radioactivity level adapted or not (part B only). Subject disposition information will be presented using the eligible subject set.

A summary table will be presented for each subject population presenting the number of subjects in each study part and cohort (part B only) at each assessment and identifying the number of subjects who withdrew over time. The reasons for exclusions from each of the populations will be listed and tabulated.

A listing of any deviations due to COVID-19 will be generated separately and a table summarizing Deviations due to COVID-19 will be produced.

The number of patients exposed to COVID-19 as well as impacted or infected (see definition below) will also be presented.



The number of visits impacted due to COVID-19 with the reasons will be summarized to assess the impact of COVID-19

A summary table will present the number of subjects who received study treatment, extent of subject exposure in the study and the study drug exposure for each study part and cohort (part B only).

The definition of the extent of subject exposure is the time interval between the first inform consent signed to the EOCT, EOAC (Part B) or EW visit completed (c.f. in Appendix 1: Derived Data). The definition of Study drug exposure (days) is the time interval between last drug intake - date of first drug intake +1 (c.f. in Appendix 1: Derived Data).

3.2.6 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the Treatment Period/LTFU and the reasons for withdrawal will be presented by study part, cohort (part B only) and overall.

In addition, the reasons of discontinuation related to COVID-19 will be summarized.

3.2.7 Demographic and baseline characteristics

All demographic and baseline characteristics will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only) and subject.

Summary statistics will be provided for demographic and baseline characteristics (age, sex, ethnicity, race, height, weight, BMI, Karnofsky performance status at screening, physical examination at baseline) by study part, cohort (part B only) and overall, for the Safety Analysis Sets.

No statistical comparison of the treatment groups will be performed.

3.2.8 Medical and surgical history

Relevant Medical or Surgical History will be coded using MedDRA Version 21.1 or higher.

Listings will present the preferred term and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, primary system organ class, preferred term and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term by study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.9 NET Cancer history

Summary statistics will be provided by study part, cohort (part B only) and overall, for the Safety Analysis Sets for initial diagnosis (GEP NET, Lung NET, Pheochromocytoma and Paraganglioma), Ki-67 index (%), Mitotic Index (/ 10 HPF) (in 3 categories: <2 mitoses, 2-20 mitoses, >20 mitoses), tumour grading (grade 1, 2 or 3), type of NET (*Non-functioning/functioning)*, histopathologic type, site of primary tumour, WHO grade, time since initial diagnostic (refer to Appendix 1: Derived Data), time since initial diagnostic by category (≥3 years versus > 3 years), time since histologically confirmed NET diagnosis (refer to Appendix 1: Derived Data), time since last relapse (refer to Appendix 1: Derived Data), time since scan of positive somatostatin receptor documentation (refer to Appendix 1: Derived Data), somatostatin receptor imaging methodology, radiopharmaceutical used for somatostatin receptor imaging, previous surgery for NET (Yes versus No), number of previous surgery for NET, and time since last previous surgery for NET (refer to Appendix 1: Derived Data), TNM residual tumour classification after surgery.

All these data will be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only) and subject.

3.2.10 Prior surgical procedures and prior Radiotherapies for NET Cancer

Number and percentage of patients having prior surgical procedures for NET cancer, as well as type of procedures will be tabulated. All data will also be listed by study part, cohort (part B only), radioactivity level adapted or not (part B only) and subject, including intent, date of surgery and time since last surgery.

Number and percentage of patients having prior radiotherapies for NET cancer, as well as type of therapies will be tabulated. All data will be also listed including intent, location of the procedure, start/end dates, total dose received and time between last radiotherapy and first study drug infusion.

3.2.11 Subject compliance

A listing will be presented for drug administration (dose, quantity, date) by cohort (part B only), radioactivity level adapted or not (part B only) and subject for each study part. Deviations from observed and scheduled times will be presented.

A listing of subjects with difficulties, delay and interruption during drug administration will be also provided.

A listing will be presented for prohibited concomitant medication for any subject who has received this prohibited medication. Subjects excluded from the Per Protocol Set due to receiving prohibited concomitant medication will be flagged (+).

3.2.12 Prior and concomitant therapies

3.2.12.1 Prior and concomitant drug therapies

Any prior or concomitant therapy or medication given to a subject for another indication within 4 weeks (28 days) before study drug administration or during study drug administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated. All recorded data will be included in data listings.

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

Medications which started and stopped before start of study treatment are considered as prior medications.

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

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.12.2 Prior and concomitant non-drug therapies

Any prior or concomitant non-drug therapy or medication given to a subject for another indication within 4 weeks (28 days) before study drug administration or during study drug administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated. All recorded data will be included in data listings.

Prior and concomitant non-drug therapies will be coded using Meddra, version 21.1 or higher.

Medications which started and stopped before start of study treatment are considered as prior medications.

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

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by cohort, subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior and concomitant non-drug therapies by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.12.3 Prior and concomitant Somatostatin Analog treatment for NET

Prior and concomitant somatostatin analog treatment for NET will be coded using WHO Drug Dictionary, version June 2016 or higher.

Somatostatin analog treatment which started and stopped before start of study treatment are considered as prior medications. Somatostatin analog treatment which started before start of study treatment but are continuing will be considered as both prior and concomitant medications.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by cohort, subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior somatostatin analog treatment for NET by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set. A similar frequency table will be provided for concomitant somatostatin analog treatment for NET.

3.2.12.4 Concomitant Protective Co-Medications for NET

Concomitant protective co-medications for NET will be coded using WHO Drug Dictionary, version June 2016 or higher.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant protective co-medications for NET by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.12.5 Prior and Concomitant Radiopharmaceutical Medications for scanning

Prior and concomitant radiopharmaceutical medications for scanning will be coded using WHO Drug Dictionary, version June 2016 or higher.

Radiopharmaceutical medications for scanning which started and stopped before start of study treatment are considered as prior medications. Radiopharmaceutical medications for scanning which started before start of study treatment but are continuing will be considered as both prior and concomitant medications.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for concomitant radiopharmaceutical medications for scanning by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.12.6 Prior Chemotherapy for NET Cancer

Prior chemotherapy for NET cancer will be coded using WHO Drug Dictionary, version June 2016 or higher.

Listings will include the therapeutic class (i.e., the second level of Anatomical Therapeutic Chemical [ATC] classification system code, that is, corresponding to the first 3 figures), preferred term (the fourth level of the ATC code, that is, corresponding to the first 5 figures) and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject id, chronological start date, stop date, therapeutic class, preferred name and verbatim name.

A frequency table of the number and percentage of subjects will be provided for prior chemotherapy for NET cancer by therapeutic class and preferred name for each study part, cohort (part B only) and overall on the Safety Analysis Set.

3.2.12.7 Concomitant Surgical Procedures

Concomitant surgical procedures will be coded using MedDRA Version 21.1 or higher.

Listings will present the preferred term and verbatim text. The listings will be sorted by study part, cohort (part B only), radioactivity level adapted or not (part B only), subject, primary system organ class, preferred term and verbatim text.

A frequency table of the number and percentage of subjects will be provided for all concomitant surgical procedures by primary system organ class and preferred term for each study part, cohort (part B only) and overall on the Safety Analysis Set.

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 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Therefore, time intervals (e.g. visit windows) have been constructed so that every observation collected can be allocated to a particular time point. If more than one record occurs within the same visit window where only one assessment is expected then the following rule should be applied: for pre-study assessments the last non-missing result prior to study drug administration should be used; for post-treatment assessments the closest non-missing result to the scheduled visit should be used.

Study part	Scheduled visit	Time interval (days)
Pre treatment (Screening)	Screening Visit	Week – 4 to -1
Active phase	Visit 1, Day 1	Day 1 (Week 0)
	Visit 1, Day 2	Day 2
	Visit 1, Day 3	Day 3
	Visit 1, Day 4	Day 4(-Day 5)
	Visit 1, Day 7	Day 7(- Day 8)
	Visit 1, Day 15	Day 15 ±2 days
	Follow-up 1 Visit 1	Week 4 (Day 29 ±5 days)
	Follow-up 2 Visit 1 – Part B only	Week 6 (Day 42±5 days)
	Visit 2, Day 1	Week 8 +2 weeks (+4 weeks in case of reversible toxicity), Day 1
	Visit 2, Day 2	Day 2
	Visit 2, Day 3	Day 3
	Visit 2, Day 4	Day 4(-Day 5)
	Visit 2, Day 7	Day 7(- Day 8)
	Visit 2, Day 15	Day 15 ±2 days
	Follow-up 1 Visit 2	Week 12 (Day 29±5)
	Follow-up 2 Visit 2 - Part B only	Week 14 (Day 42±5)
	Visit 3, Day 1	Week 16 +2 weeks (+4 weeks in case of reversible toxicity), Day 1
	Visit 3, Day 2	Day 2
	Visit 3, Day 3	Day 3
	Visit 3, Day 4	Day 4(-Day 5)
	Visit 3, Day 7	Day 7(- Day 8)
	Visit 3, Day 15	Day 15 ±2 days
	Follow-up 1 Visit 3	Week 20 (Day 29±5)
	Follow-up 2 Visit 3 – Part B only	Week 22 (Day 42±5)
End Of Core-Trial (EOCT)	End of Core-Trial Visit	Week 24 (Day 1±5)

Study part	Scheduled visit	Time interval (days)
Additional Cycles – Part B only	Additional Cycle 4, Day 1	Week 24 + 2 weeks (+4 weeks in case of reversible toxicity), Day 1
	Additional Cycle 4, Day 2	Day 2
	Additional Cycle 4, Day 3	Day 3
	Additional Cycle 4, Day 4	Day 4(-Day 5)
	Additional Cycle 4, Day 7	Day 7(- Day 8)
	Additional Cycle 4, Day 15	Day 15 ±2 days
	Follow-up 1 Additional Cycle 4	Week 28 (Day 29±5)
	Follow-up 2 Additional Cycle 4	Week 30 (Day 42±5)
	Additional Cycle 5, Day 1	Week 32 + 2 weeks (+4 weeks in case of reversible toxicity), Day 1
	Additional Cycle 5, Day 2	Day 2
	Additional Cycle 5, Day 3	Day 3
	Additional Cycle 5, Day 4	Day 4(-Day 5)
	Additional Cycle 5, Day 7	Day 7(- Day 8)
	Additional Cycle 5, Day 15	Day 15 ±2 days
	Follow-up 1 Additional Cycle 5	Week 36 (Day 29±5)
	Follow-up 2 Additional Cycle 5	Week 38 (Day 42±5)
End of Additional Cycles (EOAC)– Part B only	EOAC Visit	8 weeks after the last dose of therapy
Long term Follow-up	Long term Follow-up Visits (1-8)	every 3 months (± 2 weeks) for 2 years starting 12 weeks after EOCT/EOAC visit or early withdrawal visit, in the long-term follow-up phase
Early Withdrawal	Early Withdrawal Visit	8 weeks after the last administration study medication

Patients will be treated with three cycles of ^{177}Lu-OPS201 PRRT with an interval of 8 (+2) weeks between each cycle). If severe side effects occur, the interval can be elongated by 4 weeks. If the side effects are resolved in this time, the next treatment cycle can be initiated, if not, no further PRRT treatment will be administered and the patient will undergo the EOCT Visit.

3.2.15 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 missing values (based on subject who attended the visit), arithmetic mean, standard deviation, median and the range (minimum, maximum).

Mean, median, standard deviation and standard errors of the mean (SE) 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.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of non-missing observations. The denominator will be specified in a footnote to the tables for clarification if necessary.

Lower and upper confidence interval values will be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).

Percentiles (e.g., 25%, 75%) will be presented to one decimal place more than the raw/derived data.

If any, p-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

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].

3.2.16 Pooling of Centres

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

3.2.17 Interim analysis

1st Interim analysis

A first interim analysis will be conducted at the cut-off date of 27 September 2019 to inform the design of the chemotherapy combination study which has been added to the investigational plan.

The tables, listings and figures that will be produced for this analysis are flagged "*" in Section7.2 – List of TFLs.

2nd Interim analysis

A second interim analysis of Part B data will be conducted at the EOCT/EOAC/EW (whichever occurs last) after completion of Cohorts 3 and 6. This will provide confirmation of the peptide dose to allow future studies to be developed. It will also confirm if Cohorts 2 or 7 and 8 will be initiated.

3rd Interim analysis

A third interim analysis, including all dosimetry, safety and efficacy data, will be performed after the EOCT/EOAC/EW (whichever occurs last) when the two study parts are completed.

The interim analyses may be combined based on the overall study status and subject accrual.

The final analysis will be performed at the end of the 2-year long-term follow-up period.

Other analyses

In addition, dosimetry evaluation will be performed on an ongoing basis. After the first six subjects included have completed the study Part A (EOCT or Early Withdrawal Visit) an SRC meeting will be held before exposing the remaining subjects to the entire number of planned administrations. Safety data obtained until 8 weeks after the last administration of the 6th subject will be evaluated during this SRC. Prior to Part B, the SRC will review the safety and dosimetry data of the first six subjects included in Part A.

For Part B, a DRB meeting will be held to review the safety and radiation exposure data and decide whether to proceed with the enrolment of the next cohort dose level and the cumulative radioactivity within a cohort. Each dose escalation (both peptide and radioactivity) will be carefully evaluated by a DRB.

In addition, the SRC/DRB can be convened at any time during the trial to discuss potential safety issues. The data set to be reviewed by the SRC/DRB is specified in a specific charter.

3.2.18 Role of the Safety Review Committee (SRC) – Part A

The SRC will be composed of all Investigators, who have treated at least one subject in the study with study medication, a dosimetry expert evaluating the dosimetry data of the study, an independent hematology expert and at least one Sponsor representative. A specific charter will be developed to define roles and responsibilities, as well as the data set to be reviewed by the SRC.

This study will be performed in two parts:

Part A (15 subjects)

Initially, 6 subjects will be treated. Each patient will receive:

- 3 cycles of 4.5 GBq (target radioactivity of 4.5 GBq±10%)) ^{177}Lu-OPS201 (target dose of 300±50 µg), 8 weeks apart (+2 weeks or plus up to 4 weeks in case of AEs which have not adequately recovered).

A SRC meeting will be held before exposing the remaining 9 subjects of Part A to the entire number of planned administrations. Safety and dosimetry data from the first 6 subjects (data obtained up to 8 weeks after the last administration for each subject) will be evaluated during this SRC.

Dose limiting toxicity (DLT) definition: Investigational medicinal product (IRPP) related AEs with a severity of Grade 3 or higher are considered DLT, with the exception of hair loss, lymphopenia, nonfebrile neutropenia lasting < 4 weeks and thrombocytopenia lasting < 4 weeks.

- If DLTs occur in ≤ 33% of the patients (i.e. ≤ 2 of 6 patients), the remaining 9 patients will continue at the same radioactivity level.

- If DLTs occur in > 33% of the patients (i.e. > 2 of 6 patients), the administered radioactivity will be reduced to a cumulative radioactivity which did not lead to DLT occurrence with this frequency, e.g. the number of administrations will be reduced from 3 to 2.

Part B (up to 40 subjects)

Proceeding to next cohort will be determined by the following DLT rules based on three evaluable subjects:

- If DLTs occur in >33% of the subjects of the cohort, the next cohort will not be initiated.
- If DLTs occur in ≤33% and ≥2 of the three subjects have cumulative absorbed dose in each target organs exceeding the acceptability limits (1.5 Gy in bone marrow (BM) and 23 Gy in kidney), subjects in the next cohort will receive the same cumulative radioactivity or less than in the preceding cohort.
- If DLTs occur in ≤33% and <2 of the three subjects did not reach the cumulative absorbed dose in each target organs (1.5 Gy in BM and 23 Gy in kidney), the next cohort will be initiated as planned.

3.2.19 Role of the Data Review Board (DRB) – Part B

The following are subject stopping rules for Part B.

If any of the following occur, no further ^{177}Lu-OPS201 treatment will be administered:

- subject withdraws his/her consent to further treatment;
- cumulative kidney dose exceeds 23 Gy;
- cumulative bone marrow dose exceeds 1.5 Gy, as determined by dosimetry and dose calculation based on imaging;
- absolute neutrophil count <1.000*10^9/L (i.e. Grade 3 or higher);
- platelets <50.0*10^9/L (i.e. Grade 3 or higher);
- if one of the following medical conditions occurs (based on Common Terminology Criteria for AEs (CTCAE) v5.0 and does not resolve within four weeks (resolved=toxicity Grade 1 or recovered, and is at the discretion of the investigator):
  - eGFR of <45 mL/min/1.73m^2;
  - liver function tests (total bilirubin, aminotransferases, alkaline phosphatase and GGT) higher than Grade 3;
  - any other AE above Grade 2, except hair loss, lymphopenia, non-febrile neutropenia lasting <4 weeks and thrombocytopenia lasting <4 weeks.

The investigator can decide at his/her discretion to discontinue the treatment or to reduce the administered activity for further safety reason than those here listed above to prevent a subject from higher grade toxicity.

Before the administration of Cycles 2 and 3 these criteria must be checked. In the event of withdrawal (discontinuation) from treatment only the EOCT Visit and the Long-term Follow-up will be performed (with the EOCT Visit 12 weeks after the last administration of ^{177}Lu-OPS201).

There will be six DRBs that are defined a -priori and show in Figure 4. Each DRB described is designated a letter (A to F). The details of the decision making for each DRB is detailed in Table 9.

Figure 4 Part B Cohort Schema with DRB Designations

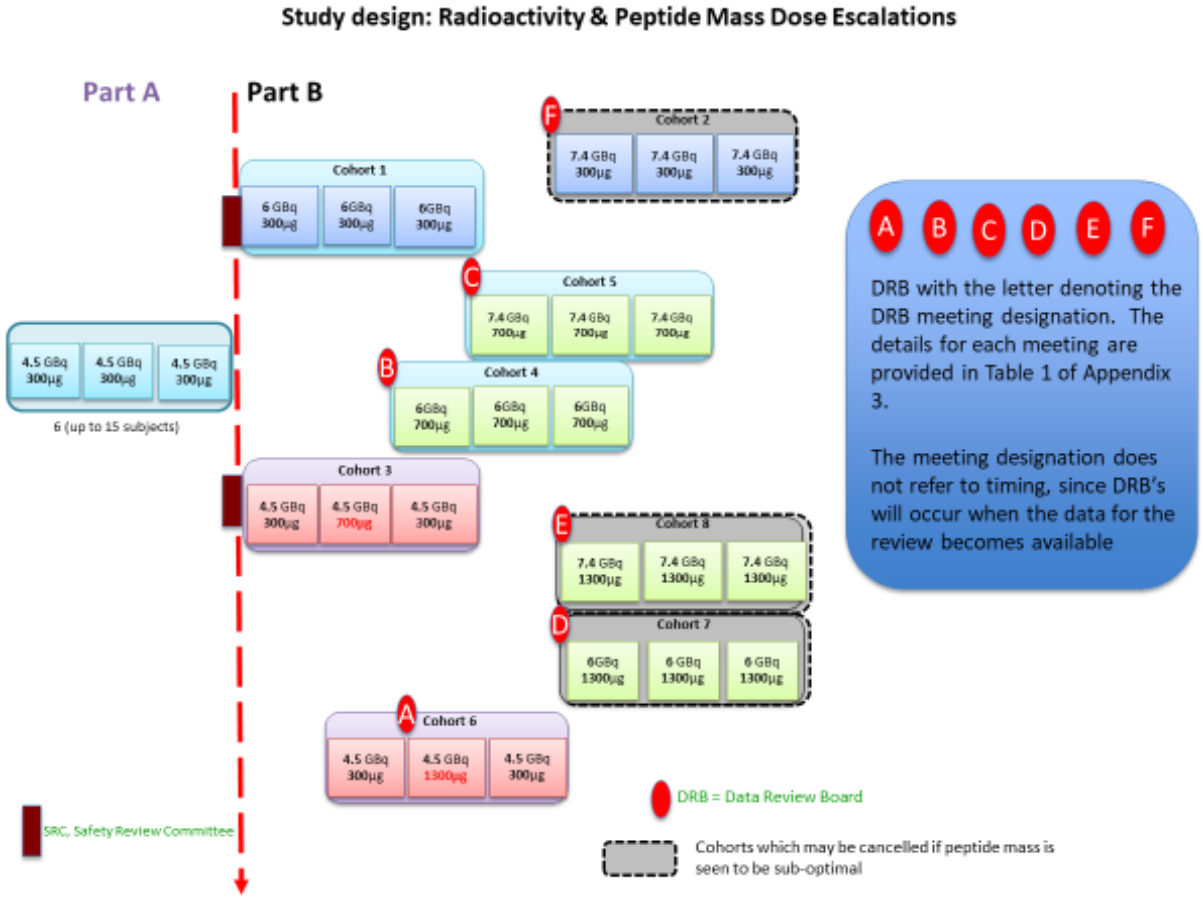


Table 9 Details of each DRB, the Timing, Question and Decision Matrix

DRB Designation[a]	Timing/data (EOC=End of cycle)	Question(s) for DRB	Decision Matrix
DRB-A	Cohort 3 First three subjects EOC-2:	Start Cohort 6 Cycle 2 with 1,300 µg peptide mass?	If >33% in Cohort 3 Cycle 2 then NO to Cohort 4.
DRB-B	Cohort 3 First three subjects, EOC-2	Start Cohort 4 with 6 GBq?	If >65% DLTs in Cohort 3 then NO to Cohort 4. If >33% and <67% DLTs in Cohort 3 Cycle 2 then wait for three more subjects in Cohort 3 Cycle 2 and re-evaluate. Otherwise start Cohort 4. *Cohort 4 will not start recruiting until Cohorts 1, 3 and 6 are fully recruited*
DRB-C	Cohort 4 EOC-1	Start Cohort 5? Continue Cohort 4?	If >33% DLTs in Cohort 4 then NO to Cohort 5. If >33% DLTs in Cohort 4 then STOP. Evaluate peptide mass dosing and lesion receptor saturation. Evaluate next cohort to start and activity dosing.
DRB-D	Cohort 6 EOC-3 All subjects Cohort 4 EOC-1	Start Cohort 7?	If >33% DLT in Cohort 6 Cycle 2 NO to Cohort 7 AND If lesion receptor saturation in Cohort 6 Cycle 2, then no to Cohort 7 AND If >33% DLTs and <67% DLTs in Cohort 4 and receptor modelling suggests Cohort 7 mass dose safer, then start Cohort 7, otherwise no.
DRB-E	Cohort 6 EOC-3 All subjects Cohort 5 EOC-1	Start Cohort 8?	If >33% DLT in Cohort 6 Cycle 2 NO to Cohort 8 AND If lesion receptor saturation in Cohort 6 Cycle 2, then no to Cohort 8 AND If >33% DLTs <67% DLTs in Cohort 5 and receptor modelling suggests Cohort 8 mass dose safer, then start Cohort 8, otherwise no.
DRB-F	Cohort 1 EOC-3 and Cohort 3 EOC-3 and Cohort 5 EOC-1	Start Cohort 2?	If mass dose modelling suggest 300 ug is optimal AND If >33% DLTs in Cohort 1, AND If >33% DLTs in Cohort 5 Start Cohort 2

DLT=dose limiting toxicity; DRB=data review board; EOC=end of cycle; GBq=gigabecquerel.
Note: At each DRB, safety data available from all cohorts will be evaluated to inform decision making.
a although the DRBs are written in alphabetical sequence this is not a chronological order; each one will be conducted when data becomes available which is dependent on subject recruitment. An ad-hoc DRB can be called to ensure continuity of dosing. Although three completed subjects are required for each completed cycle for evaluation, all available subject data in that cohort will be used (e.g. If five subjects are enrolled and all five complete the end of a cycle prior to the DRB, then all five sets of data will be evaluated).

This cumulative activity in the cohort being evaluated will be determined by the following DLT rules:

- If, in the preceding cohort after the third administration of ^{177}Lu-OPS201, DLTs occur in >33% of three subjects (i.e. >1out of the three to five subjects), the activity for the next cohort will be reduced to a cumulative administered activity which did not lead to DLT occurrence with this frequency.
- If, in the preceding cohort after the third administration of 6GBq ^{177}Lu-OPS201, DLTs occur in ≤33% of three subjects and ≥2 of the three subjects have a cumulative absorbed

dose in each target organ exceeding the acceptability limits (1.5 Gy in BM and 23 Gy in kidney), subjects in the next cohort will receive the same cumulative activity or less than in the preceding cohort.

- If, in the preceding cohort after the third administration of 6GBq ^{177}Lu-OPS201, DLTs occur in ≤33% of the three subjects and less than two of the three subjects did not reach the cumulative absorbed dose in each target organ (1.5 Gy in BM and 23 Gy in kidney), the activity in the next cohort will be escalated up to 7.4 GBq per administration, as detailed in the table above

Data Review Board

- the DRB will consist of a team of "permanent" decision makers (the core team);
- principal investigators may participate, present and listen in;
- all final decisions will be made by the core team;
- the number of DRB meetings may change as needed and can be called upon rapidly if there is a safety issue of concern in a cohort;
- the aim is to have all meetings via conference call, but if the timing does not allow for this, then it can be conducted via email exchange or two conference calls with split attendees;
- a DRB charter will be developed with further details.

3.2.20 Covariates and analysis of subgroups

No adjustment on covariate and no subgroups analysis are planned to be performed.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows 7 or higher version.

4.2 Software

All tables, listings and figures will be produced, and statistical analysis performed using SAS® version 9.2 or higher version. All output will be in Microsoft Word Format.

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. Covance SOP CCI [redacted] provides an overview of the development of such SAS® programs and describes the quality control procedures that must be performed for all SAS® programs and outputs. 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. CCI [redacted] will be prepared to document the methods of validation.

Copies of the internal QC forms produced for the validation process and the Covance's sign-off forms will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

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

5 CHANGES FROM PROTOCOL

Dosimetry sections:

Cumulative absorbed dose to the lesions (Gy) has been added as dosimetry endpoint.

AE section:

AESI definition was updated to "any TEAE related to ^{177}Lu-OPS201 which occurs the day of ^{177}Lu-OPS201 administration (same date as ^{177}Lu-OPS201 administration and at any cycle). "

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7 APPENDICES

7.1 Appendix 1: Derived Data

The following derived data will be calculated and included in the listings:

(1) **BMI**

BMI (kg/m2) will be derived as Weight (kg)/[Height(cm)/100]^2 and rounded to the nearest decimal. Underweight is defined as BMI < 18.5, normal as between 18.5 and 25, and overweight as ≥ 25.

(2) **Body Surface Area**

Body Surface Area (m^2) will be derived with the Mosteller formula as (Weight (kg) * Height(cm) / 3600) ½ and rounded to the nearest decimal.

(3) **Changes from baseline**

Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

(4) **Adverse event duration**

If the start and end dates of the adverse event are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time – start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date)+1 and presented in days. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date)+1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) [i.e.: ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004].

(5) **Time since last dose for adverse event**

If the start date of the adverse event is identical to the date of last administration, then"<1" day will be presented with the time to onset in hh:mm recorded in the eCRF if it is available. If

times are available, the time will be calculated as (start date/time – last administration date/time) and presented in days hh:mm. If at least one time is missing and if the time to onset is greater than 24 hours then it will be calculated as (start date - last administration date)+1 and presented in days. If the start date and the associated information do not allow to state about the last dose received (partial start date or start at administration day without knowing if it started before or after the drug intake), all the possible time since last dose will be presented [i.e.: if a subject received a daily administration and reported an AE at second administration day but without indication about before or after the drug intake the time since last dose will be as "2 / <1"]. If the start date is partial, the time since last dose will be presented as an superior inequality (i.e.: for an AE started in FEB2004 after the only administration performed on 31JAN2004, the time since last dose will be as "≥2" days). If the start date is missing the time since last dose will not be presented although the AE will be assigned to each dose received before its end date.

(6) **Days since last dose for study drug administration or discontinued subject**

The days since last dose for study drug administration will be calculated as (drug administration date/time - previous administration date/time)+1 and presented in days hh:mm. The days since last dose for discontinued subject will be calculated as (discontinued date - last administration date)+1 and presented in days.

(7) **Time since initial diagnosis** (months) will be calculated as (screening date - date of initial diagnosis + 1)/30.4375

(8) **Time since histologically confirmed NET diagnosis** (months) will be calculated as (screening date - date of histologically confirmed NET diagnosis + 1)/30.4375

(9) **Time since scan of positive somatostatin receptor documentation** (months) will be calculated as (screening date - date of scan of positive somatostatin receptor documentation + 1)/30.4375

(10) **Time since last relapse/ time since last previous surgery for NET** (months) will be calculated as (screening date - date of last relapse/surgery + 1)/30.4375

(11) **Study exposure**

Study exposure in days will be calculated as (last visit attended - first inform consent signed date) + 1.

(12) **Duration of Study Drug Exposure**

Duration (days) = (last dose or infusion date - first dose or infusion date +1)

(13) **Delay in injection**

A delay in injection is defined as an injection performed more than one day after the scheduled injection date.

The number of days of delay will be positive and calculated as the difference between the actual injection date and the scheduled injection date.

(14) **Injection performed in anticipation**

An injection performed in anticipation is defined by an injection performed more than 1 day in advance compared to the scheduled date.

The number of days of anticipated injections will be positive and calculated as the difference between the scheduled injection date and the actual injection date.

(15) **Concomitant therapy duration**

If times are available, the duration of concomitant treatments/physiotherapy etc. will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) +1. If the recorded end date is CONT. (for continuing) then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e.: ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

(16) **Study day**

Study day will be defined as '-1' for the day prior to treatment and as '1' for the day of treatment (i.e. day 0 does not exist).

(17) **For quantitative statistics of biological values**, a **standardization** method will be used in order to take into account the differences between the reference ranges of the different laboratories:

In a general way, standardised values will be assessed using the following formula:

$$X_{St.} = X_{LRef} + \left(X_{URef} - X_{LRef}\right)\frac{X - X_L}{X_U - X_L}$$

where X = measured value,

XL = lower limit value for the laboratory of the measured value,

XU = upper limit value for the laboratory of the measured value,

XLRef. = lower limit value for the laboratory chosen as a reference,

XURef. = upper limit value for the laboratory chosen as a reference,

If a standardised value is negative it will be replaced by 0.

There is no missing value for any reference value.

(18) **A nadir** for a subject is defined as the lowest laboratory value during the whole treatment period (all cycles combined) among all infusions for that subject and a nadir for a cycle is defined as the lowest laboratory value in that cycle. The day to nadir in a cycle is the number of days between the nadir and the first date of study medication intake of that cycle.

(19) Whole body absorbed dose

AbsorbedDose_WholeBody [Gy]= $AUC_{WholeBody}$ [Bq.s]X E_{beta} / $Weight_{WholeBody}$ [kg]

With E_{beta} = 2.3664E-14 J.Bq-1.s-1.

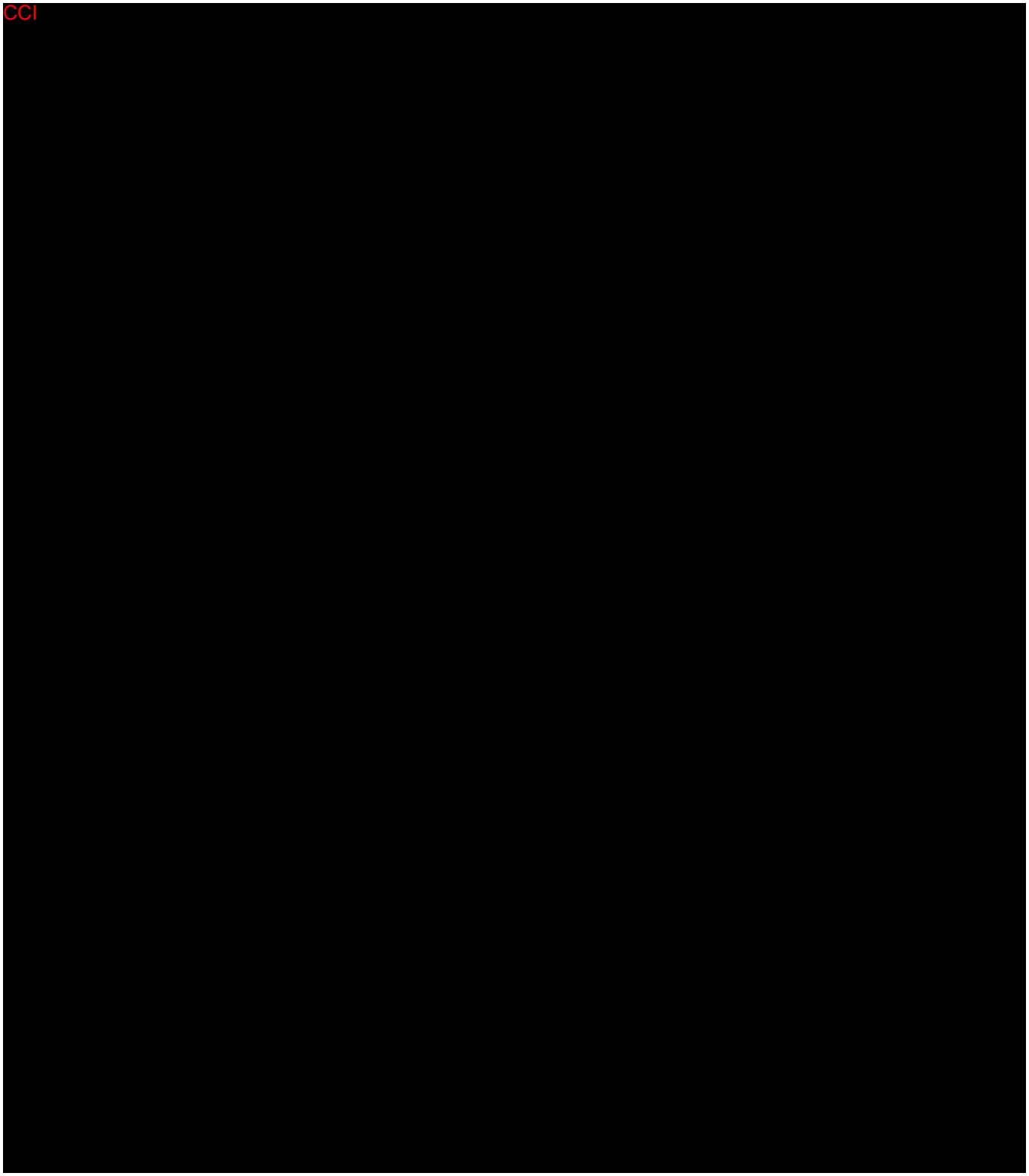
(20) Whole body specific absorbed dose

Specific_AbsorbedDose_WholeBody [Gy/GBq] = AbsorbedDose_WholeBody [Gy]/ Radioactivity_administered [GBq]

(21) Amount excreted (Ae) for cold PK urine sample

Ae [ng] = ConcentrationOPS201_urine (ng/mL) x volume urine collected (mL)

CCI



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