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)

STUDY PROTOCOL

STUDY number: OPS-C-001 / D-FR-01072-001

^{177}Lu-OPS201

EudraCT number: 2015-002867-41

ClinicalTrials.gov number: NCT02592707

Version 10.0: 10 August 2020

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol OPS-C-001/D-FR-01072-001 entitled "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)" with Amendment 10.0. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:

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Sponsor's Representative Signature:

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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol OPS-C-001/D-FR-01072-001 entitled "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)" with Amendment 10.0. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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SUMMARY OF CHANGES

The current version of the protocol was released on 10 August 2020 and includes Amendment 10.0. For all protocol amendments, amendment forms were prepared and are provided in the appendices listed in Table 1. All modifications (except minor changes) are presented in the appendices.

Table 1 List of Protocol Amendments

Version number	Release date	Amendment form
3	29 April 2016	Appendix 6
4	04 October 2016	Appendix 7
5	03 November 2017	Appendix 8
6	27 February 2018	Appendix 9
7	24 July 2018	Appendix 10
8	07 May 2019	Appendix 11
9	13 August 2019	Appendix 12
10	10 August 2020	Appendix 13

SYNOPSIS

Name of sponsor/company: IPSEN PHARMA

Name of finished product: ^{177}Lu-OPS201 - ^{177}Lu-satoreotide tetraxetan

Name of active ingredient(s): ^{177}Lu-OPS201 - INN for OPS201 is satoreotide tetraxetan

Title of study: 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)

Study number: OPS-C-001 / D-FR-01072-001

Number of planned centres: 20

Planned study period:	**Phase of development**:
January 2016 to November 2022	Phase I/II

Study type: Interventional, open-label, safety, tolerability, biodistribution, dosimetry and preliminary efficacy study

Objectives:

Primary study objective:

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 NETs (including phaechromocytomas and paragangliomas).

Secondary study 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 RECIST (Response Evaluation Criteria in Solid Tumours) (version) v1.1 status.
- To evaluate the influence of ^{177}Lu-OPS201 PRRT on the subject's quality of life.

Exploratory study objectives

CCI [redacted]

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

CCI [redacted]

CCI

Study hypotheses: ^{177}Lu-OPS201 will be sufficiently safe to permit further clinical investigation when administered in previously treated subjects with unresectable gastroenteropancreatic (GEP) NETs, lung NETs and malignant, unresectable pheochromocytoma or paraganglioma.

Increase of peptide mass doses leads to improved tumour to background ratio for ^{177}Lu-OPS201 with a possible positive impact on the safety profile

Methodology:

NOTE: the study medication (OPS201), and all the biosamples (including blood, urine and biopsy material taken on study) are all radioactive and all due precautions are to be taken to protect subjects, study staff, persons preparing, transporting or analysing materials and members of the public.

This is a multi-centre, open-label study to evaluate the safety and tolerability of ^{177}Lu-OPS201 for the treatment of NETs.

In total, up to 55 subjects with histologically confirmed NETs and a positive somatostatin receptor scan (SRS) will receive three administrations of ^{177}Lu-OPS201 at 8-week intervals (+2 weeks, or up to +4 weeks in case of adverse events (AEs) which have not adequately recovered). The study will be performed in two parts (Part A and Part B) and has a safety review committee (SRC, Part A) and a data review board (DRB, Part B). In Part B, up to two additional cycles of ^{177}Lu-OPS201 can be administered if the subject continues to meet the criteria outlined in Section 6.4.2 and the subject has clinical benefit (defined as complete response (CR), partial response (PR) or stable disease (SD)). The additional cycles are optional and must be discussed with the sponsor before administration.

Subjects will be recruited at the participating study centres specialised in the diagnosis and treatment of NETs. For each cycle, subjects will attend the following visits (Figure 1):

- Screening Visit: Up to 4 weeks before the first administration of ^{177}Lu-OPS201, subjects who provided signed informed consent will undergo a Screening Visit to check eligibility criteria. A contrast enhanced computed tomography (CT)/magnetic resonance imaging (MRI) scan will be performed as well as a screening SRS (unless the latter has already been performed within 6 months of Visit 1 Day 1). Eligibility read for SRS and CT/MRI scan will be performed locally at screening. However, all images, including SRS, will be sent to the imaging core laboratory for later evaluation.

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 plus 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 tests 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 scan to monitor the RECIST v1.1 status and tumour volume changes.
- Visit 3: 8 weeks after Visit 2 Day 1 (+2 weeks or plus 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 assessed.

- 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 6.0 comes into effect will receive a CT/MRI scan to monitor the RECIST v1.1 status and tumour volume. CT/MRI scan images will be sent to the imaging core laboratory for later evaluation.

Part B

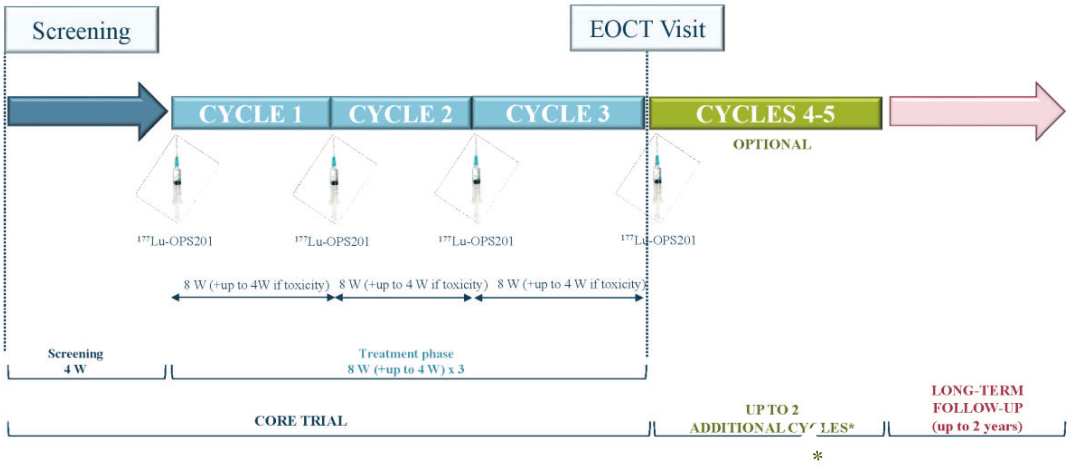
- Visit 1: On Visit 1 Day 1, subjects will receive the first administration of ^{177}Lu-OPS201 followed by safety and extended dosimetry evaluations over 8 days, with additional laboratory safety tests repeated at Day 15 (±2 days). At Week 4 (Day 29±5 days), Week 6 (Day 42±5 days) (i.e. Follow-up Visit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

In case of additional cycles administration, subjects will have the same safety and dosimetry follow-up as during the core treatment cycles and up to the end of additional cycles (EOAC) or early withdrawal (EW). 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 long-term follow-up period will start after the EOCT/EOAC/EW Visit. Long-term efficacy follow-up will be assessed every 3 months (±2 weeks) until whichever occurs first: documented disease progression (radiological or clinical as per the investigator's judgment), 2 years after the EOCT/EOAC/EW Visit, withdrawal of consent, lost to follow-up or death. Long-term safety follow-up will continue 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, all subjects will be invited to participate in a safety surveillance study.

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

Part A and Part B of the Phase I study

The study will be performed in two parts:

- 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.
- As a radioactivity and peptide mass dose escalation are planned in Part B, up to 40 subjects are planned to be treated. The Part A SRC will decide, based on safety and dosimetry data from Part A, if a radioactivity and/or peptide dose escalation in Part B is applicable or if the radioactivity has to be adapted (this can be higher/lower than 4.5 GBq or maintained at the same dose, but not exceeding 7.4 GBq per dose). In Part B, the objective of the DRB is 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 (see Appendix 3). Each dose escalation (both peptide and radioactivity) will be evaluated by the DRB as detailed in Appendix 3. As new safety and dosimetry information becomes available in other cohorts, this data will be used to evaluate the on-going cohorts and the subject dosing within the cohorts.

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, whereas the long-term follow-up will last 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, whereas the long-term follow-up will last for up to 2 years after the EOCT/EOAC/EW Visit.

Cohorts, dose(s) and route of administration

Part A:

Initially, six subjects will be treated in Part A. Each subject will receive three cycles of 4.5 GBq (target radioactivity of 4.5 GBq±10%) ^{177}Lu-OPS201 (target peptide mass dose of 300±50 µg), 8 weeks apart (+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 in Part A to the entire number of planned administrations. Safety and dosimetry data from the first six 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 in Part A: investigational radiopharmaceutical product (IRPP) related AEs with a severity of Grade 3 or higher are considered DLTs, with the exception of hair loss, lymphopenia, nonfebrile neutropenia lasting <4 weeks and thrombocytopenia lasting <4 weeks.

- If DLTs occur in ≤33% of subjects, the remaining nine subjects will continue at the same radioactivity level.
- If DLTs occur in >33% of subjects, 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 three to two.

After treatment completion of the sixth subject (Part A), the SRC will decide, based on the safety and dosimetry data from Part A, if a radioactivity escalation is applicable in Part B.

Part B:

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 characterised as shown in Table 2.

Table 2 Radioactivity and Peptide Mass Dose in Each Cohort and Cycle

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 (Cycles 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 (Cycles 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

C=cycle; GBq=gigaBecquerel; IRPP=investigational radiopharmaceutical product.
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.

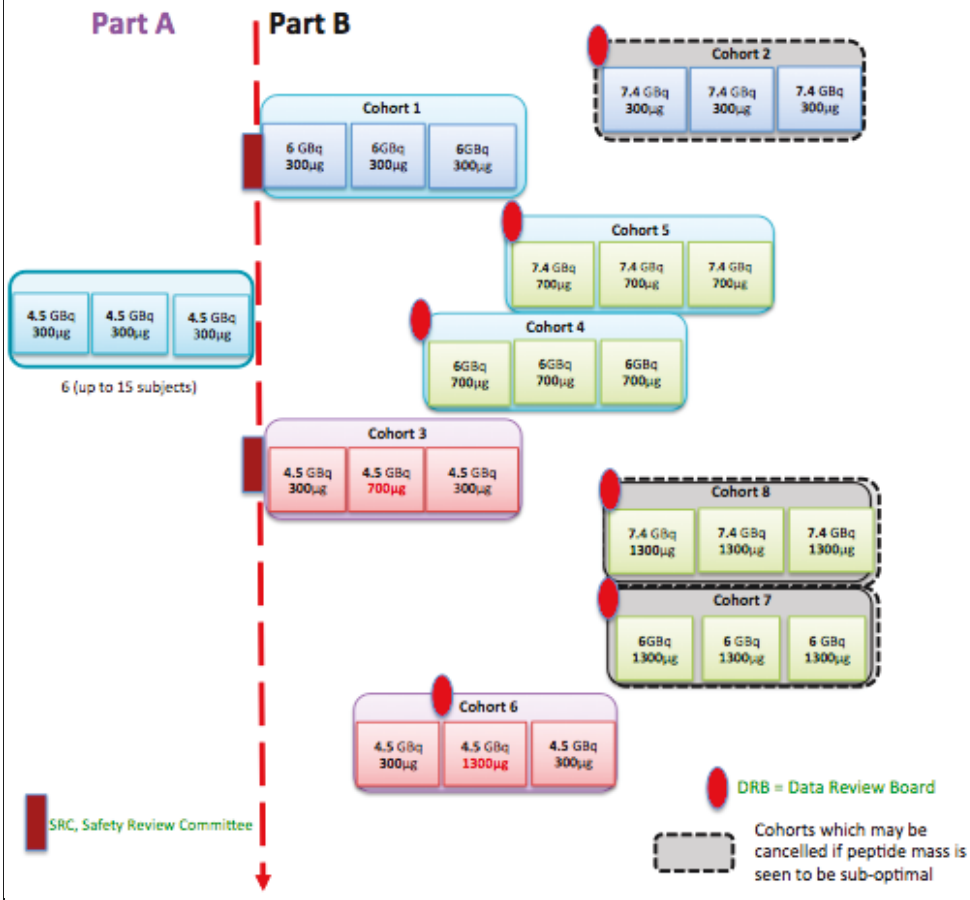
The schema for the dosing and cohorts in Part B is shown in Figure 2.

In each cohort, each subject will receive three cycles of the defined radioactivity and peptide mass dose of ^{177}Lu-OPS201. 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 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 6.4.2 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 2 Study Design - Part B



DRB=data review board; GBq=gigaBecquerel; SRC=safety review committee.
Priority for the conduct of the cohorts is as follows: Cohorts 1 and 3, Cohort 6, Cohort 4, Cohort 5. 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).

Radioactivity evaluation (Part A)

In Part A, a cumulative radioactivity of 13.5 GBq (4.5 GBq/cycle × three cycles) with a peptide mass dose of 300 µg will be evaluated (Table 2).

In Part B, the radioactivity and peptide mass dosing for each cycle in each cohort is illustrated in Table 2.

Radioactivity escalation (Cohorts 1 and 2 – Part B)

Cohort 1 will investigate a radioactivity of 6 GBq/cycle (cumulative radioactivity 18 GBq) with the same peptide mass dose as in Part A (300 µg) for three cycles (Table 2).

Once the third subject of Cohort 1 has completed at least two cycles, if no safety signal is observed and if the subjects did not reach the cumulative absorbed dose in each of the target

organs, Cohort 2 (300 µg; 7.4 GBq/cycle; cumulative 22.2 GBq; Table 2) will be initiated (see priority classification in Figure 2). However, if improved safety regarding DLTs is seen with increased peptide mass, Cohort 2 (300 µg; 7.4 GBq/cycle; cumulative 22.2 GBq) may be delayed until experience is gained with the 7.4 GBq dose at the higher peptide mass (700 µg). If optimal peptide mass is evaluated to be >300 µg then this cohort will not be opened.

Intra-individual peptide mass dose evaluation (Cohorts 3 and 6 – Part B)

Cohorts 3 and 6 will allow the intra-individual evaluation of peptide mass. In both Cohorts 3 and 6, subjects will receive the same cumulative radioactivity as in Part A (4.5 GBq/cycle; cumulative, 13.5 GBq; Table 2). The associated peptide mass dose will also be the same (300 µg) in Cycles 1 and 3, and will be increased to 700 µg in Cohort 3 and 1300 µg in Cohort 6 during Cycle 2.

Peptide mass dose escalation (Cohorts 4 and 5 and optional Cohorts 7 and 8 – Part B)

In Cohort 4, subjects will receive 6 GBq/cycle (cumulative 18 GBq) with a peptide mass dose of 700 µg, for three cycles (Table 2). After one cycle, if no safety signal is observed in Cohort 4, Cohort 5 will be initiated. In Cohort 5, subjects will receive 7.4 GBq/cycle (cumulative, 22.2 GBq) with a peptide masse dose of 700 µg, for three cycles (Table 2).

Cohorts 7 and 8 will be cancelled if ssr2 saturation is seen with peptide mass dose of 700µg and 1300 µg in Cohort 3 or 6 and/or if there are other safety signals (Table 2). There will be no further dose escalation of OPS201 peptide after 1300 µg.

The dose escalation rules

The DRB will consist of a team of "permanent" decision makers (the core team), including selected principal investigators and Ipsen personnel. All final decisions will be made by the core team. The number of DRB meetings may change as needed and the DRB 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 the meeting can be conducted via email exchange or two conference calls with split attendees. A DRB charter will be developed with further details. Ad-hoc DRBs can be convened at any time during the trial.

Dose escalation (peptide mass dose and radioactivity, see Figure 2) will primarily be decided based on the clinical and safety data of the subjects.

DLT definition in Part B: IRPP related AEs with a severity of Grade 3 or higher are considered DLTs, with the exception of hair loss, lymphopenia, nonfebrile neutropenia lasting <4 weeks and thrombocytopenia lasting <4 weeks.

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

- if DLTs occur in >33% of subjects in the cohort, the next cohort will not be initiated.
- if DLTs occur in ≤33% and ≥2 of the three subjects have a cumulative absorbed dose in each target organ 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 organ (1.5 Gy in BM and 23 Gy in kidney), the next cohort will be initiated as planned.

Each dose escalation (both peptide and radioactivity) will be carefully evaluated by the DRB. As safety and dosimetry information becomes available in other cohorts, this data will be used to evaluate the on-going cohorts and the subjects' dosing within the cohorts.

The DRB can make a recommendation as to the radioactivity dosing for the next cohort. This could include continuing the current cohort to complete five subjects for review. Based on the overall safety results, the DRB can also decide to start earlier or delay cohorts depending on the information available. Notification will be given to the principal investigators if this is to occur, with the rationale, as well as to the institutional review board (IRB)/ethics committee (EC).

Number of subjects planned:

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 six subjects and up to 15 subjects.
- Part B: a minimum of 25 subjects and up to 40 subjects.

For Part B dose escalation, it is anticipated that approximately 40 subjects will be included, in up to eight escalation steps (cohorts). Three to five subjects will be treated per cohort in order to yield a minimum of three completed subjects for three cycles of treatment. For Cohorts 3 and 6, eight to 10 subjects will be treated per cohort to yield a minimum of eight completed subjects. Any cohort can be closed for safety issues before all the subjects are completed.

Diagnosis and criteria for inclusion:

Inclusion criteria:

(1) Written informed consent.

(2) Subjects of either gender, aged ≥18 years.

(3) Women of childbearing potential (not surgically sterile or less than 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after the last dose. Acceptable methods of contraception include abstinence, or double contraception: steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method (intrauterine device, condom, etc.).

(4) Male subjects must use a medically accepted method of contraception and must agree to continue the use of this method for the duration of the study and for 6 months after the last radioactivity administration.

(5) Karnofsky performance score ≥60.

(6) Life expectancy of at least 6 months.

(7) Histologically confirmed diagnosis of:

- unresectable GEP NET (Grade I and Grade II according to World Health Organization (WHO) classification (2010, see Annex 01), functioning and nonfunctioning).
- unresectable “typical lung carcinoid” or “atypical lung carcinoid” are acceptable (with the exception of Large Cell Bronchial Neuroendocrine Neoplasms and Small Cell Lung Cancers) (Caplin 2015).
- malignant, unresectable pheochromocytoma or paraganglioma.
  - subjects, who have histologically confirmed NET, but no clear localisation of their primary tumour, can be included.

(8) Documentation of progressive disease (PD) based on RECIST v1.1 under prior antitumour therapy within 6 months of Visit 1 Day 1 (although the progression might have occurred more than 6 months before Visit 1 Day1). Subjects should not have

received further antitumour therapy once disease progression is documented. All images should be sent to the imaging core laboratory.

(9) In countries where sunitinib or everolimus are marketed, subjects with GEP NET and lung NET will be progressive under this prior antitumour treatment for the respective indication. Subjects not suitable for everolimus/sunitinib therapy according to a tumour board decision (or comparable local practice) may also be enrolled into the study. Subjects having everolimus/sunitinib therapy should have a wash-out phase of ≥4 weeks before the first treatment.

(10) Measurable disease based on RECIST v1.1.:

(11) For Part A: Confirmed presence of sstr on technically evaluable tumour lesions documented by a positive SRS*. If this has not been performed within 6 months of Visit 1 Day 1, then it must be repeated during screening
* presence of at least one lesion that is ≥20 mm in the longest dimension (as measured on correlative CT or MRI scan) and with a maximum standardised uptake value (SUV_{max}) of ≥2 × the SUV_{mean} of the liver background on ^{68}Ga-positron-emission tomography (PET) imaging or a score of "3" or "4" according to the Krenning scale on single photon emission computed tomography (SPECT) imaging.

For Part B: Confirmed presence of sstr on technically evaluable tumour lesions documented by a positive SRS*. If this has not been performed within 6 months of Visit 1 Day 1, then it must be repeated during screening.

*presence of at least two lesions that are ≥20 mm in the longest dimension (as measured on correlative CT or MRI scan) with an SUV_{max} of ≥2× the SUV_{mean} of the liver background on ^{68}Ga-PET imaging or a score of "3" or "4" according to the Krenning scale on SPECT imaging.

(12) Calculated glomerular filtration rate (GFR) ≥55 mL/min.

(13) Blood test results as follows:

- Leukocytes: $\geq 4*10^9$/L.
- Erythrocytes: $\geq 3.5*10^{12}$/L
- Platelets: $\geq 100*10^9$/L
- Albumin: >30 g/L.
- Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase: ≤5 times upper limit of normal (ULN).
- Bilirubin: ≤2 times ULN (2×1.1 mg/dL).

Exclusion criteria:

Eligible subjects must not have any of the following conditions:

(1) Known hypersensitivity to ^{177}Lu, DOTA, JR11 or to any of the excipients of ^{177}Lu-OPS201.

(2) Any previous PRRT.

(3) Diagnosis of thymic NET.

(4) Presence of active infection at screening, or history of serious infection within the previous 6 weeks.

(5) Administration of any other investigational medicinal product (IMP) within 60 days prior to entry (Visit 1 Day 1).

(6) Prior or planned administration of a therapeutic radiopharmaceutical within 8 half-lives of the radionuclide including any time during the current study.

(7) Any extensive radiotherapy ≤3 months before first IRPP administration.

(8) Chemotherapy ≤3 months before first IRPP administration.

(9) For Part B: Nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study as assessed by the investigator.

(10a) Pregnant or breast-feeding women. A serum pregnancy test will be performed at the start of the study for all female subjects of childbearing potential (i.e. not surgically sterile or up to 2 years postmenopausal).

(11) Any uncontrolled significant medical, psychiatric or surgical condition (active infection (including subject with known hepatitis B or hepatitis C and subjects with known human immunodeficiency virus (HIV) positive), unstable angina pectoris, cardiac arrhythmia, poorly controlled hypertension, poorly controlled diabetes mellitus (glycated haemoglobin (HbA1c) ≥9%), uncontrolled congestive heart disease, etc.) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety or that would limit compliance with the objectives and assessments of the study. Note: the subject should be able to tolerate high volume load.

(12) Current history of any malignancy other than NET within 5 years of enrolment except for fully-resected non-melanoma skin cancer or cervical cancer in situ.

(13) Any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

Test product, dose, mode of administration:

Investigational radiopharmaceutical product (IRPP), ^{177}Lu-OPS201:

^{177}Lu-OPS201 is a therapeutic radiopharmaceutical product with three main components, namely (a) ^{177}Lutetium (^{177}Lu), a β- and γ- emitting radionuclide with a half-life of 6.65 days; (b) DOTA, (international nonproprietary name: tetraxetan) a chemical chelator group; and (c) JR11, an antagonistic somatostatin analogue which binds to sstr2 on NET cells (OPS201=DOTA-JR11). All doses are presented as a sterile aqueous solution, equivalent to the respective dose of radioactivity, for intravenous (i.v.) infusion.

Therapeutic administrations:

At each PRRT cycle (Visits 1 to 3 and additional cycles, if any) 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 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.

Note: Prior to adoption of the protocol version 8.0, infusion was to be administered over 30 to 60 minutes.

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.

Duration of treatment:

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 will last 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. After the long-term follow-up period is completed, all subjects will be invited to participate in a safety surveillance study.

Reference therapy, dose and mode of administration:

Not applicable

Criteria for evaluation (endpoints):

Safety endpoints

- Frequency 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

Biodistribution and radioactive PK of the radiopharmaceutical endpoints

- Maximal uptake (%) at the target lesions
- Maximal uptake (%) in discernible organs and blood
- Area under the curve (AUC) of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs, target lesions and blood
- Terminal half-life of radioactivity concentrations of the radiopharmaceutical in blood

Radiation dosimetry endpoints

- Organs receiving the highest absorbed dose
- Specific absorbed dose to the target lesion (Gy/GBq)
- Specific absorbed dose per organ (Gy/GBq)
- Cumulative absorbed organ doses (Gy)

OPS201 PK endpoints

- If OPS201 levels are measurable in plasma and urine, 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), cumulative amount of unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma (CL_R)) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of OPS201 and on the individual urine concentrations.

CCI [redacted]

Secondary efficacy endpoints

The following secondary efficacy variables will be assessed:

- Objective tumour response based on RECIST v1.1 (CT/MRI scan) by calculating best overall response (BOR), overall response rate (ORR) and disease control rate (DCR)

- Progression free survival (PFS) based on RECIST v1.1

Influence of ^{177}Lu-OPS201 PRRT on the Quality of Life of the Subjects

- Quality of Life Questionnaire ((QLQ)-C30; GI.NET21) change from baseline to EOCT

CCI

[redacted]

Statistical methods:

All data will be analysed by descriptive statistical methods, as follows:

Primary variable (safety and tolerability)

Frequency and/or descriptive summaries of abnormal findings in physical examination, vital signs, ECG (12-lead and Holter), and clinical laboratory parameters; reports of SAEs and AEs will be summarised by severity and relationship; frequency and type of DLTs; use of concomitant medications.

Secondary variables

(a) Biodistribution and PK of the radiopharmaceutical:

- Maximal uptake (%) at the target lesion
- Maximal uptake (%) in discernible organs and blood
- AUC of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs, target lesion and blood
- Terminal half-life of radioactivity concentrations of the radiopharmaceutical in blood

(b) Radiation dosimetry:

- Organs receiving the highest absorbed dose
- Specific absorbed dose to the target lesion (Gy/GBq)
- Specific absorbed dose per organ (Gy/GBq)
- Cumulative absorbed organ doses (Gy)

(c) Pharmacokinetics:

- If OPS201 levels are measurable in plasma and/or urine, PK parameters of OPS201 (including, but not limited to, C_{max}, AUC, $t_{1/2}$, CL, Vd, Ae and CL_R) will be derived using a non-compartmental approach

(d) Efficacy (tumour response):

- Objective tumour response based on RECIST v1.1 (CT/MRI scan) by calculating BOR, ORR and DCR
- PFS based on RECIST v1.1

(e) Influence of ^{177}Lu-OPS201 PRRT on the quality of life:

- Quality of Life Questionnaire (QLQ-C30; GI.NET21)

CCI

[redacted]

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
3D	Three-dimensional
^{68}Ga	Positron-emitting isotope of Gallium
^{68}Ga-OPS202	^{68}Ga-labeled somatostatin antagonist for diagnostic imaging
^{90}Y	^{90}Yttrium
^{177}Lu	^{177}Lutetium
^{177}Lu-OPS201	Study medication, ^{177}Lu-labeled somatostatin antagonist for PRRT
AC	Atypical carcinoid
ADL	Activity of daily living
ADR	Adverse drug reaction
Ae	Cumulative amount of unchanged drug excreted into the urine
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under the whole blood or plasma/serum concentration time curve
BM	Bone marrow
BOR	Best overall response
CA	Competent authority
cfDNA	Cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations (United States of America)
Cg A	Chromogranin A
CL	Apparent total body clearance of the drug from plasma
CL_R	Renal clearance of the drug from plasma
C_{max}	Maximum observed concentration
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract research organisation
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DCR	Disease control rate

ABBREVIATION	Wording Definition
DLT	Dose limiting toxicity
DOTA	Tetraxetan, a chemical chelator group
DOM	Dosimetry operational manual
DoR	Duration of response
DRB	Data review board
DTPA	Diethylene triamine penta-acetic acid
EANM	European Association of Nuclear Medicine
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOAC	End of additional cycles
EOCT	End of Core Trial
EU	European Union
EW	Early withdrawal
FDA	Food and Drug Administration
fT4	Free thyroxine
GBq	Gigabecquerel, SI unit of radioactivity
GCP	Good Clinical Practice
GEP	Gastroenteropancreatic
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GST	Glutathione S-transferase
Gy	Gray, SI unit of absorbed radiation dose
HbA1c	Glycated haemoglobin
HCG	Human chorionic gonadotropin
HEK	Human embryonic kidney
HPLC	High-performance liquid chromatography
HIV	Human immunodeficiency virus
IAEA	International Atomic Energy Agency
IA/ROI	Injected activity/region of interest

ABBREVIATION	Wording Definition
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
IDMS	Isotope dilution mass spectrometry
IEC	Independent ethics committee
IGF	Insulin-like growth factor
IIT	Investigator-initiated trial
IMP	Investigational medicinal product
IRB	Institutional review board
IRPP	Investigational radiopharmaceutical product
IRR	Infusion related reaction
ISF	Investigator's site file
ITT	Intent-to-treat
ITT-DAS	Intent-to-treat dosimetry analysis set
i.v.	Intravenous
JR11	Somatostatin analogue peptide JR11
K_d	dissociation constant
KIM-1	Kidney injury molecule-1
LCNEC	Large cell neuroendocrine carcinoma
MBq	Megabecquerel, SI unit of radioactivity
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MEN-1	Multiple endocrine neoplasia 1
mRECIST	Modified RECIST
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MS/MS	Tandem mass spectrometry
NCI	National Cancer Institute
NET	Neuroendocrine tumour
NODAGA	A chemical chelator group
NOS	Not otherwise specified
NSE	Neuron-specific enolase
OPS201	Somatostatin analogue peptide JR11 coupled to DOTA

ABBREVIATION	Wording Definition
OPS202	Somatostatin analogue peptide JR11 coupled to NODEGA
ORR	Objective response rate
PD	Progressive disease
PET	Positron-emission tomography
PFS	Progression free survival
PK	Pharmacokinetic(s)
PP	Per protocol
PP-DAS	Per protocol-dosimetry analysis set
PR	Partial response
PRRT	Peptide receptor radionuclide therapy
PT	Preferred term
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SCLC	Small cell lung cancer
SD	Stable disease
SDV	Source document verification
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SOC	System organ class
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
SRC	Safety review committee
SRS	Somatostatin receptor scintigraphy
SSA	Somatostatin analogue
sstr	Somatostatin receptor
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardised uptake value
SUV_{max}	Maximum standardised uptake value
SUV_{mean}	Mean standardised uptake value
t½	Elimination half-life
TAC	Time activity curve

ABBREVIATION	Wording Definition
TC	Typical carcinoid
TEAE	Treatment emergent adverse event
TGR	Tumour growth rate
TMF	Trial master file
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US(A)	United States (of America)
Vd	Apparent volume of distribution
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Neuroendocrine tumours (NETs) are as heterogeneous in their clinical appearance as they are rare in occurrence.[1] Improvements in diagnosis by advanced endoscopic and radiological imaging have led to an increase in reported incidence rates in the United States of America (USA) from 1.09 in 100,000 in 1973 to 5.25 in 100,000 in 2004.[2] They primarily appear as carcinoid tumours of bronchopulmonary or gastrointestinal origin representing 0.46% of malignant diseases in general.[3]

1.1.1 Gastroenteropancreatic Neuroendocrine Tumours (GEP NETs)

Gastroenteropancreatic (GEP) NETs arise from local totipotent stem cells of the diffuse neuroendocrine system in the gastrointestinal tract and pancreas rather than from the neural crest, as it was previously thought.[4] There are at least 13 gastrointestinal neuroendocrine cell types, producing different sets of bioactive peptides or amines as serotonin, somatostatin, histamine or gastrin, stored in secretory vesicles. Therefore, vesicular proteins such as chromogranin A (Cg A) and synaptophysin are markers of neuroendocrine cells.

In most cases GEP NETs are slow-growing tumours, which remain unnoticed until the occurrence of mass effects or predominantly hepatic metastases. Functioning tumours can secrete a variety of bioactive peptides and neuro-amines which produce distinct syndromes such as carcinoid syndrome, hypoglycaemic syndrome or Zollinger-Ellison syndrome.[5] Although the clinical symptoms of functioning tumours (e.g. flushing, diarrhoea and asthma in carcinoid syndrome) are a burden for the quality of life of the patient, they have the beneficial effect of allowing an early diagnosis and better prognosis. However, the majority (90%) of GEP NETs develop in a nonfunctioning form, leading to delayed diagnosis and metastatic disease.[6]

The diagnosis of GEP NETs is driven by a high index of suspicion. In general, diagnosis is based on clinical presentation, hormone assays, markers such as Cg A, and pathology. These are enhanced by a variety of imaging techniques such as endoscopic ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), selective angiography (with hormonal sampling), nuclear imaging as somatostatin receptor (sstr) single photon emission computed tomography (SPECT), bone scanning and various intraoperative methods. However, due to their heterogeneity, no imaging method covers the whole variety of GEP NETs. The prognosis of GEP NET patients depends on the characteristic of the tumour. In well-differentiated neuroendocrine carcinoma the 5-year survival can be 60% to 100%, whereas in regional disease and with distant metastases it decreases to 40% and 29%, respectively.[1]

The treatment of GEP NETs is highly individualised, based on tumour burden and symptoms. In slow growing tumours, surgery can be a method of cure, for instance in insulinomas. In more severe cases, surgery or embolisation can be applied as a method of cytoreduction. For functioning tumours, apart from the removal or reduction of tumour mass, the management of the symptoms is a major goal of treatment, leading to an increase in quality of life for the patients.

1.1.2 Lung Neuroendocrine Tumours

Lung NETs have a low incidence which has been increasing in the past three decades mostly due to better detection methods and increased use of imaging techniques.[7, 8, 9]

The 2004 World Health Organization (WHO) classification includes four types of lung NET: small cell lung cancer (SCLC), large cell neuroendocrine carcinoma (LCNEC), typical carcinoid (TC) and atypical carcinoid (AC).[10] Neuroendocrine tumours represent 25% of primary lung cancers and the most common lung NET is SCLC (20%), followed by LCNEC (3%) and carcinoids. Lung carcinoid tumours account for 5% of most common multiple

endocrine neoplasia 1 (MEN-1) neoplasm. SCLC and LCNEC are both associated with smoking while carcinoids have no predilection for smoking history.[11]

Most bronchial NETs are located in major bronchi (70%); therefore, most of these are detected due to symptoms such as haemoptysis, cough, infections, fever and unilateral wheezing while peripheral NETs are usually discovered incidentally.[12, 13] Differently from GEP NET, lung carcinoids are rarely functioning and hypersecreting (2% versus 10% in GEP NET).[11, 14] In a small percentage of patients with Cushing's syndrome the cause is production of adrenocorticotrophic hormone from a bronchial or thymic NET.[7, 8, 13]

As for GEP NET, diagnosis is based on specific markers (e.g. p-Cg A, p-neuron-specific enolase (NSE)), imaging techniques including somatostatin receptor scintigraphy (SRS) and positron-emission tomography (PET) scanning (fluorodeoxyglucose PET for SCLC and LCNEC), bronchoscopy and MEN-1 genetic screening when indicated.[7, 8]. Prognosis of lung NET varies depending on the histological type: 5-year survival for SCLC is less than 5%, for LCNEC is 15% to 57% and for carcinoids varies from a high 5-year survival rate for TC (>87%) to a poorer prognosis for AC since these are more aggressive (5-year survival rate of 44% to 78%).[7, 8, 11, 13]

The treatment of lung NET varies depending on the tumour type: SCLC, since considered a nonsurgical disease, is mainly treated with chemotherapy regimens and radiotherapy; for LCNEC there is still no consensus on the clinical management since it is quite rare; carcinoid tumours are primarily a surgical disease not very sensitive to radiotherapy and chemotherapy. Peptide receptor radionuclide therapy (PRRT) showed some promising results in tumour growth but remains investigational.[7, 8, 11, 15]

1.1.3 Pheochromocytoma-Paraganglioma

According to the 2004 WHO classification of endocrine tumours, pheochromocytoma is a malignancy arising from the adrenal medulla catecholamine-producing chromaffin cells, while paraganglioma arises from the same cells in the extra-adrenal paraganglia.[16] Pheochromocytoma and paragangliomas occur in ≤0.1% of hypertensive patients and in 4% of patients is fortuitously discovered as adrenal mass.[17] These tumours may cause symptoms such as hypertension, arrhythmia and/or hyperglycaemia by releasing catecholamines. Only a small portion of pheochromocytomas are malignant (10% to 17%) with lymph nodes, visceral, or bone metastases.[18, 19]

Pheochromocytomas may be associated with genetically inherited diseases such as familial pheochromocytoma-paraganglioma syndromes, multiple endocrine neoplasia type 2, neurofibromatosis 1 and von Hippel-Lindau disease, or may be sporadic[18]

Besides imaging studies, diagnosis currently is mostly based on plasma or urinary metanephrine levels which are diagnostic if results are at least four times the upper limit of normal (ULN).[20] No staging system is available for pheochromocytoma and the overall 5-year survival rate is between 34% and 60% depending on tumour size, location and succinate dehydrogenase subunit B mutation status.[16, 18]

At present, no cure for malignant pheochromocytoma or paraganglioma is available and no reliable tumour markers have been identified to diagnose malignancy or assess prognosis. The main therapeutic strategies are wait and see, therapeutic embolisation, radiofrequency ablation, systemic chemotherapy and radionuclide therapies. Currently, 131I-labeled metaiodobenzylguanidine therapy is the single most used adjuvant therapy after surgical treatment of malignant pheochromocytomas.[16, 18]

1.1.4 Somatostatin Analogues

One approach to ease the symptoms of functioning NETs is the application of somatostatin analogues (SSAs). Physiologically, somatostatin inhibits the secretion of endocrine hormones or bioactive amines including insulin, glucagon and gastrin[21] depending on receptor and cell type. Somatostatin binds to the five different G-protein coupled receptors, sstr 1 to 5. Around 80% of GEP NETs express sstr subtypes (1 to 5) in well-differentiated forms.[6, 22, 23]

Somatostatin binds all its natural receptors with high affinity but has a short half-life in vivo. Synthetic SSAs are less prone to degradation by peptidases and have an increased half-life but differing receptor affinities, with high affinities mainly to sstr2 and partially sstr5. Their biological activities are prolonged to 1.5 to 2 hours versus 1 to 2 minutes with the natural peptide.[24] Somatostatin analogues are widely used in clinical practice and are known to ameliorate the symptoms of carcinoid syndrome. Apart from this symptomatic treatment, SSAs are reported to have a beneficial effect on tumour growth. This antiproliferative effect has been attributed to cell cycle arrest, induction of apoptosis, antiangiogenic inhibition of vascular endothelial growth factor, immunomodulation and further secondary effects connected to the physiological somatostatin function. For the two approved SSAs octreotide (PROMID study, Novartis) and lanreotide (CLARINET study, Ipsen), large scale, controlled phase III studies proved disease stabilisation and prolonged progression free survival (PFS) in patients with metastasised NETs, including functioning and nonfunctioning tumours.[25]

1.1.5 Radiolabelled Somatostatin Analogues

The clinical impact of SSAs is not limited to their pharmacological activity as the peptides can also be used for in vivo receptor targeting. Radiolabelled octreotide is applied for the imaging of NETs expressing sstr2, sstr3 and sstr5. The localisation of the primary tumour and its metastases is crucial for the management of the malignant disease. As a diagnostic SSA of the first generation, octreotide is fused to the chelator diethylene triamine penta-acetic acid (DTPA) and can be labelled with ^{111}Indium (OctreoScan^{TM}) for the imaging of its gamma radiation in SRS using a gamma camera or SPECT.

Second generation SSA peptides, like DOTA-TOC and DOTA-TATE, show higher affinities to distinct sstrs and by utilising DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) as a chelator can be labelled with the β emitter ^{68}Gallium as PET/CT tracers. The PET/CT scan with second generation peptides showed good diagnostic performance. In a meta-analysis of published studies, PET/CT was shown to provide higher sensitivity and detect more lesions than SRS.

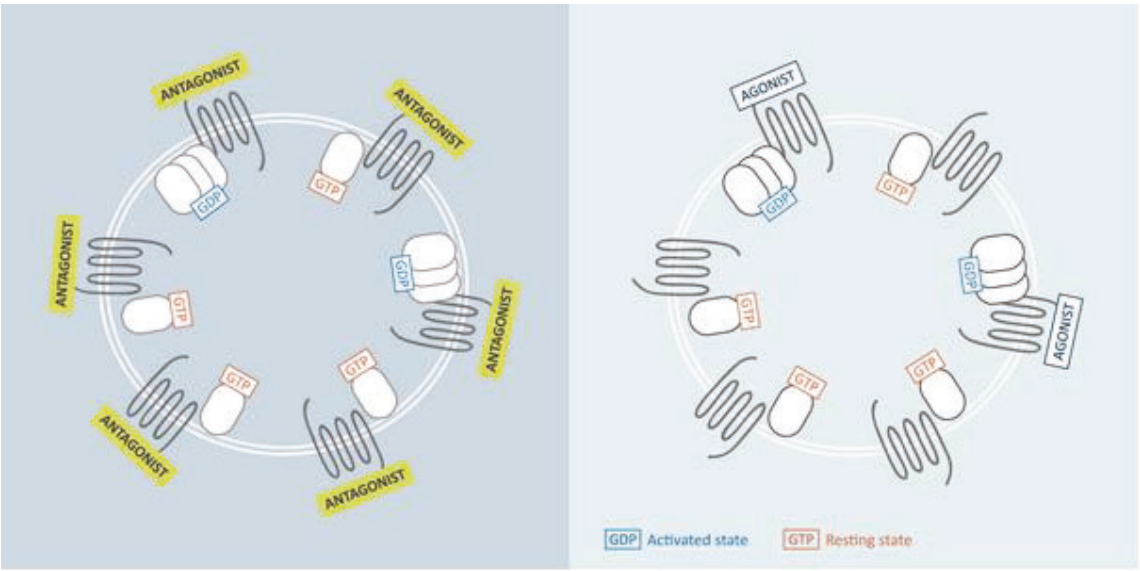
Depending on the nuclide, radiolabelled SSAs can be used as tracers for imaging or for PRRT. Labelled with a β-emitting radionuclide such as ^{90}Yttrium (^{90}Y) or ^{177}Lutetium (^{177}Lu), DOTA-TOC and DOTA-TATE have entered clinical practice in many leading centres in the field of NETs. In contrast to the very nonspecific toxic effects of conventional chemotherapy, PRRT specifically targets malignant NET cells and has been proven to be safe and effective.[26, 27]

1.1.6 Antagonistic Somatostatin Analogues

Agonists, like octreotide or DOTA-TOC and DOTA-TATE, were preferred for in vivo receptor targeting since they trigger receptor internalisation and thereby transport the radionuclide into the cell, while antagonists do not.[28] However, recent studies suggest that antagonists could be even more effective. Although internalisation is not induced by high affinity antagonists, an increased tumour uptake may be observed for the antagonist ^{111}In-DOTA-BASS (half maximal inhibitory concentration (IC_{50}) (sstr2)=9.4 nM) compared to the agonist ^{111}In-DTPA-TATE (IC_{50} (sstr2)=1.3 nM).[29] Scatchard plots demonstrated many more sites labelled by the

antagonist compared to the agonist. It is hypothesised that the antagonist binds to a variety of receptor conformations independent of the activation state, whereas the agonist depends on the bound guanine nucleotide of the G-protein coupled receptor (Figure 1).[30] This increase in binding sites correlates with a higher tumour-to-tissue ratio of the SRS utilising the antagonist.[29]

Figure 3 Superior Binding Behaviour of Antagonistic Somatostatin Analogues



The new class of antagonistic peptides (left) is independent of the sstr activation state (G-protein phosphorylation). Therefore, they utilise many more binding sites on the tumour cell surface, while agonistic peptides (right) only target activated receptors. [30]

These preclinical findings were confirmed in a first clinical application of an sstr antagonist used for SRS imaging in 5 NET patients. A comparison of the antagonist ^{111}In-DOTA-BASS to the approved ^{111}In DTPA-octreotide (OctreoScan^{TM}/Mallinckrodt) in SRS showed an up to 4.1 times higher uptake in the tumour and an up to 5.2 times higher tumour-to-kidney uptake ratio. Moreover, out of 28 lesions identified in CT scans, only 17 could be detected by SRS with the agonist while 25 were verified in the antagonistic scan.[31]

Following the hypothesis of favourable antagonistic SSAs the third generation peptide DOTA-JR11 (OPS201) was developed, demonstrating higher affinity than DOTA-BASS and selectivity for sstr2 (0.7±0.12 nM).[32]

Somatostatin analogue peptide JR11 is currently developed for a theranostic approach based on the same peptide somatostatin antagonist. In the diagnostic compound OPS202, it is coupled to the chelator NODAGA and can be labelled with the radionuclide ^{68}Gallium. The therapeutic peptide OPS201 contains the chelating agent DOTA and can be labelled with isotopes like ^{90}Y or ^{177}Lu. In this phase I/II study, the clinical safety and tolerability, as well as the efficacy of a PRRT treatment with three cycles of the study medication, the ^{177}Lu-labelled somatostatin antagonist for PRRT (^{177}Lu-OPS201) will be evaluated.

1.2 General Considerations for ^{177}Lu-OPS201

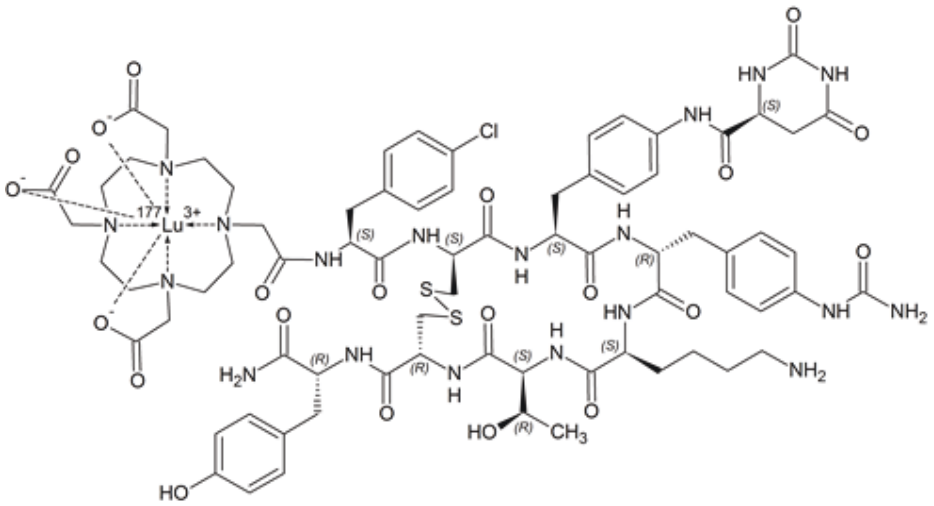
The chemical name and structure of the study medication ^{177}Lu-OPS201 are given below.

1.2.1 Chemical Name:

Lutetium-^{177}(3+),S^2,S^7-cyclo[N-{4,7,10-tricarboxymethyl-1,4,7,10-tetraaza-cyclododecan-1-yl-acetyl}-4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4*S*)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide]

1.2.2 Chemical Structure:

Figure 4 Chemical Structure of ^{177}Lu-OPS201



^{177}Lu-OPS201 has three main components, namely the SSA JR11, the chemical chelator group DOTA and the β emitter ^{177}Lutetium (^{177}Lu).

JR11 is an SAA with the chemical formula Cpa-D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys-D-Tyr-NH2. Due to its antagonistic properties, binding to sstrs does not activate any physiological cell response (e.g. signal transduction via phosphorylation, receptor internalisation) as is observed with agonists.

DOTA (international nonproprietary name: tetraxetan) is a chelating agent with the chemical formula 1,4,7,10 tetraazacyclododecane-1,4,7,10-tetraacetic acid. DOTA is already in use in clinical studies for example in the monoclonal antibody, ^{90}Y-clivatuzumab tetraxetan, for the radiotherapy of pancreatic cancer which is currently in phase III.[33]

^{177}Lu is a β- and γ- emitting radionuclide. It has a half-life of 6.65 days and maximum and mean β particle energies of 0.498 MeV and 0.134 MeV, respectively. This reflects in the maximum and mean soft-tissue penetration depths of 1.7 mm and 0.23 mm, respectively. [35] The two main gamma emission lines are 113 keV (6% relative abundance) and 208 keV (10.4% relative abundance), [34] which allows post treatment imaging and dosimetry assessments.[35]

Table 3 Radiophysical Characteristics of ^{177}Lutetium

Physical half-life t½	6.65 days
Decay product	^{177}Hf
Maximum β- particle energy	0.498 MeV
Mean β-particle energy	0.133 MeV
Mean tissue penetration	0.23 mm
Maximum tissue penetration	1.7 mm
Main gamma emission lines	113 keV (6.2%) 208 keV (10.4%)

^{177}Hf=hafnium-177; keV=kiloelectron volt.

In preclinical and clinical assessments, OPS201 showed increased tumour uptake and improved tumour to-tissue uptake ratios compared to agonistic SSAs. The elongated residence time at the tumour suits well to the physical half-life of ^{177}Lu, which makes it an ideal compound for the PRRT of GEP NET lesions.

1.3 Previous Experience with Study Drug

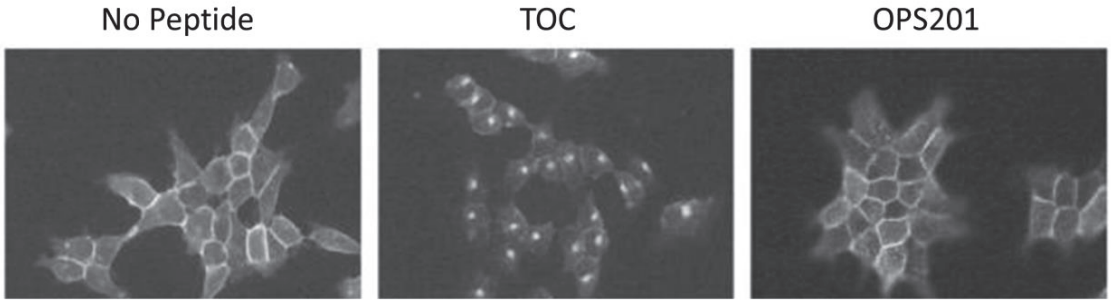
1.3.1 Preclinical Studies

1.3.1.1 Antagonistic Behaviour – Internalisation and Calcium Release

In contrast to receptor antagonists, the binding of agonists to sstr leads to receptor internalisation and activation of intracellular signal transduction pathways. Ultimately, sstr activation produces a wide range of physiological effects throughout the body including the inhibition of the secretion of many hormones.[36]

An internalisation assay based on sstr2 immunofluorescence microscopy with sstr2-overexpressing human embryonic kidneys (HEK) cells was performed to determine whether OPS201 (compound 31 in citation) acts as an agonist or antagonist. In comparison to the control analogue TOC, OPS201 did not induce internalisation of sstr2 receptors (Figure 5). Furthermore, unlike the agonist it did not activate calcium signalling in a calcium release assay and therefore acts as a receptor antagonist.[32]

Figure 5 Internalisation of sstr2 After Receptor Stimulation with Somatostatin Analogues



Adapted from Cescato et al 2008 [32]

1.3.1.2 Somatostatin Receptor 2 Binding

The sstr subtype sstr2 plays a major role in the tumour biology of GEP NETs.[37] Therefore, the receptor binding affinities of OPS201 and ^{nat}Lu-OPS201 were analysed in sstr2-overexpressing HEK cells by autoradiography. ^{nat}Lu-OPS201 coupling to DOTA retained a high sstr2 affinity comparable to the OPS201 compound without metal (see Table 4). ^{nat}Ga-DOTA-TATE was used as a reference compound.[38]

Table 4 Sstr2 Receptor Binding Affinities [38]

Compound	sstr2 (IC_{50}, nmol/L)[a]
OPS201 (DOTA-JR11)	0.72±0.12
^{nat}Lu-OPS201 (^{nat}Lu-DOTA-JR11)	0.73±0.15
Reference agonist ^{nat}Ga-DOTA-TATE	0.2±0.04

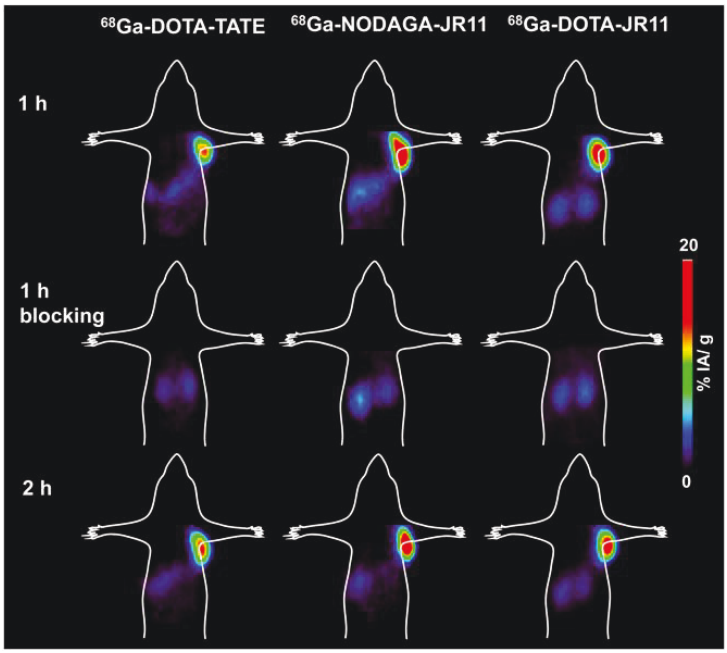
DOTA=tetraxetan; Ga=gallium; JR11=Somatostatin analogue peptide JR11; OPS201=Somatostatin analogue peptide JR11 coupled to DOTA; sstr2=somatostatin receptor subtype-2; TATE=tyrosine-3-octreotate
a IC_{50} values are shown as mean±standard error of the mean (SEM) (nmol/L)

The antagonistic peptide ^{nat}Lu-OPS201 showed slightly weaker affinity to the sstr2 compared to the strongest agonistic peptide Ga-DOTA-TATE. Nevertheless, due to the higher number of available binding sites (activated and nonactivated receptors) on the tumour cells accessible to antagonistic peptides, a higher uptake of ^{177}Lu-OPS201 in sstr2 tumours is possible [29,32] and could be shown in preclinical and clinical in vivo studies.

1.3.2 Preclinical In Vivo Results

1.3.2.1 Biodistribution

Figure 6 In Vivo Biodistribution

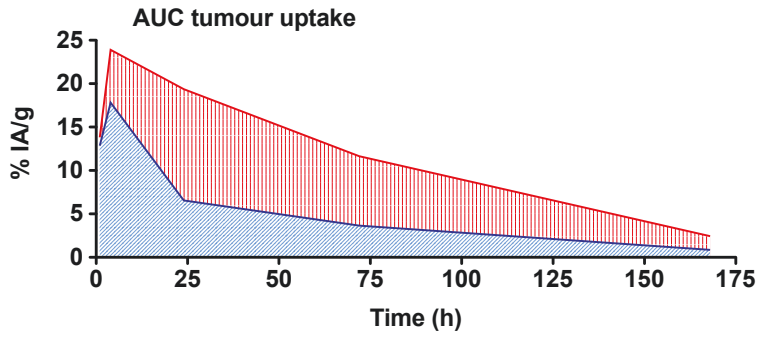


Small-animal PET images (coronal sections) of mice bearing HEK-HSST2 tumour injected with ^{68}Ga DOTATATE, ^{68}Ga-OPS201, and ^{68}Ga-OPS202 (NODAGA-JR11)[38]

In vivo biodistribution studies comparing the ^{68}Ga-DOTATATE agonist with ^{68}Ga-DOTA-JR11 and ^{68}Ga NODAGA-JR11 showed not only that the JR11 antagonist radio-ligands were superior to the agonist ligands, but also that ^{68}Ga-labeled somatostatin antagonist for diagnostic imaging (^{68}Ga-OPS202, NODAGA-JR11) was the tracer of choice for PET imaging and preferable to ^{68}Ga-OPS201 (DOTA-JR11) in transplanted HEK293-hSST2 tumours in mice (Figure 6).[38] For this reason, ^{68}Ga-OPS202 (NODAGA-JR11) was chosen for the clinical development as a PET/CT imaging compound. CCI [redacted]

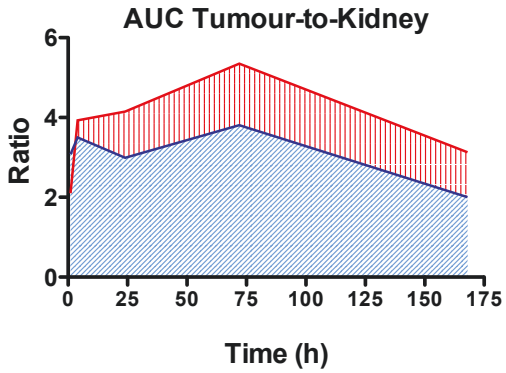
In another preclinical study on HEK-hSST2 xenografts in nude mice, OPS201 was radiolabelled with ^{68}Ga for PET imaging and with ^{177}Lu for therapy. ^{68}Ga-OPS201 and ^{177}Lu-OPS201 were compared head-to-head with ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE in terms of receptor affinity, tumour uptake, image contrast and pharmacokinetics (PK). Pharmacokinetics, mass-dependence as well as PET and SPECT/CT imaging studies were performed.[39].

Figure 7 AUC Tumour Uptake



AUC=area under the curve; h=hour
Red: ^{177}Lu-OPS201, Blue: ^{177}Lu-DOTA-TATE [39]

Figure 8 AUC Tumour-to-Kidney

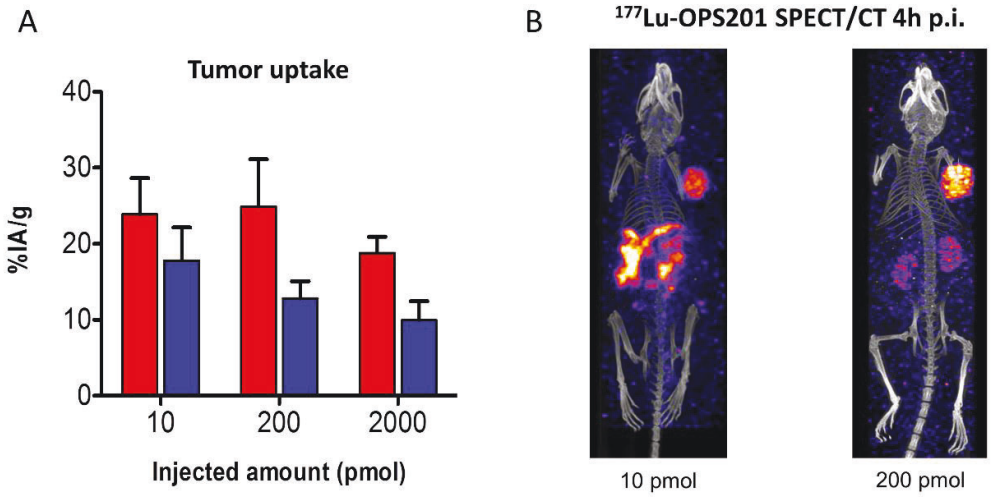


AUC=area under the curve; h=hour
Red: ^{177}Lu-OPS201, Blue: ^{177}Lu-DOTA-TATE [39]

With ^{68}Ga-OPS201 a 1.3-fold higher tumour uptake and with ^{177}Lu-OPS201 an approximately 35% higher tumour uptake (Figure 7) could be observed in comparison to the DOTA-TATE equivalent. For ^{177}Lu-OPS201 the highest uptake was monitored at 4 hours after the injection. For ^{177}Lu-OPS201 the mean tumour residence time was 19.1 hours, compared to 7.5 hours for ^{177}Lu-DOTA-TATE, resulting in a 2.5 times higher tumour dose for the antagonist than for the agonist. Despite a 1.8-fold increased kidney dose, the therapeutic index defined as tumour-to-kidney dose ratio showed a 34% increase in favour of ^{177}Lu-OPS201 (Figure 8).

With an escalation of the used peptide dose from 10 pmol to, 200 pmol to 2000 pmol of ^{177}Lu-OPS201, no relevant saturation effect in the tumour could be achieved while the background saturation significantly decreased (Figure 9).

Figure 9 Peptide Dose Escalation



A) tumour uptake of red: ^{177}Lu-OPS201 and blue ^{177}Lu-DOTA-TATE in % injected radioactivity with increasing peptide mass doses. for ^{177}Lu-OPS201 no saturation effect is shown, while for ^{177}Lu-DOTA-TATE the tumour uptake decreases with increasing peptide concentrations. B) SPECT/CT images of HEK-HSST2 xenografts in nude mice with ^{177}Lu-OPS201 in two different peptide mass doses.[39]

Tissue distribution of ^{177}Lu-OPS201 was also evaluated in sstr2-expressing tumour bearing mice (human SCLC H69) at peptide doses of 0.5 µg (300 pmol), 1 µg (600 pmol) and 2 µg (1200 pmol).[40] Injection of 0.5 µg and 1 µg of ^{177}Lu-OPS201 resulted in the highest tumour uptake. High uptake was also seen in the kidneys, as a consequence of urinary excretion, and in the sstr2-expressing pancreas and stomach. Kidney, stomach and pancreas radioactivity decreased relatively quickly, whereas tumour uptake remained twice as long. Dosimetry calculations resulted in a tumour radiation dose of 1.8±0.7 Gy/MBq after injection of 0.5 µg of OPS201. The tumour, pancreas, and stomach doses were considerably reduced with higher peptide amount (1.9, 2.9 and 3.2-fold reduction, from 0.5 to 2.0 µg of peptide, respectively), whereas the kidney dose remained constant. In this study, the optimal peptide dose appeared to be ≤1 µg in H69 tumour-bearing mice with the highest absorbed dose to the tumour compared to the other tissues.

1.3.2.2 In Vivo Pharmacology, Activity on Tumour Growth in an SCLC Model

^{177}Lu-OPS201 demonstrated its potency to reduce tumour growth in one animal model, NCI-H69 xenograft in mice SCLC model. In the therapy experiment, mice with subcutaneous H69 xenografts were intravenously injected with 0.5 mg/30 MBq (megabecquerels) of ^{177}Lu-OPS201, 0.5 mg/30 MBq of ^{177}Lu-DOTA-TATE, or 200 mL of injection fluid. Animals treated with ^{177}Lu-OPS201 showed a decrease in tumour size up to 45±7 days after cell implantation after which tumour regrowth occurred. For ^{177}Lu-DOTA-TATE, tumour regrowth was already observed 41±2 days after injection of the radiotracer. Furthermore, median survival rates were 43.5, 61, and 71 days for the control group, the ^{177}Lu-DOTA-TATE group, and the ^{177}Lu-OPS201 treated group, respectively.[40]

1.3.3 Nonclinical Safety (Toxicity Test) of OPS201

CCI

CCI

[redacted]

1.3.4 Dosimetry in Pigs

CCI

[redacted]

CCI

[redacted]

CCI

1.3.6 Adverse Effects

CCI

First insights into potential side effects of a PRRT with ^{177}Lu-OPS201 in humans could be gained in a preliminary therapeutic study under compassionate use at the University Hospital in Freiburg. Four patients with histologically proven, progressively metastasised inoperable NETs, and limited treatment options due to chronic Grade 2 or 3 kidney disease, were treated with two to three cycles of ^{177}Lu-OPS201 (1.87 GBq to 5.89 GBq) at an interval of 8 weeks.[31] These first cases of PRRT with ^{177}Lu-OPS201 showed promising results. Regarding adverse events (AEs), one patient experienced a short episode of flush just after injection of ^{177}Lu-OPS201. Another patient developed Grade 3 thrombocytopenia (41,000/mm^3), which completely recovered within 8 weeks after injection of ^{177}Lu-OPS201. There was no relevant decrease of tubular kidney function within 12 months of follow-up. Also, creatinine levels did not significantly change before and approximately 12 months after treatment. In summary, the first treated patients showed promising clinical results without any adverse reactions of concern.

Since the expected side effects of ^{177}Lu-OPS201 are caused by the administered radioactivity rather than by toxic effects of the peptide itself, known adverse reactions comparable to PRRTs with the established agonistic SSAs ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-TOC are anticipated.[35]

1.3.6.1 Acute Reaction

Adverse events such as nausea, headache and rarely vomiting due to metabolic acidosis induced by the amino acid coadministration do occur in the majority of subjects.

The PRRT may exacerbate the syndromes related to the respective functional tumours, due to the sudden massive release of the hormones and receptor stimulation. The clinical manifestation is dependent on the specific hormone involved.

1.3.6.2 Delayed Reactions

Delayed adverse reactions of PRRTs have been reported mainly for kidney function and blood building cells in the bone marrow.[35]

1.3.6.2.1 Renal Toxicity

To safeguard the kidneys as the dose-limiting organs from the activities normally reached with PRRT, kidney protection measures such as infusion of cationic amino acids must be performed. However, in some cases, despite kidney protection, loss of kidney function can occur after PRRT, with a creatinine clearance loss of about 3.8% per year for ^{177}Lu-DOTA-TATE. Delayed renal toxicity was observed more frequently in subjects with predisposing risk factors including longstanding and poorly controlled hypertension and diabetes mellitus.

1.3.6.2.2 Bone Marrow Toxicity

Severe (Grade 3 and 4), mostly reversible, acute bone marrow toxicity is observed in only 2% to 3% of cycles with ^{177}Lu-DOTA-TATE. Nevertheless, sporadic cases of myelodysplastic syndrome or overt acute myelogenous leukaemia have been reported.

1.4 Phase I Investigator Study

An investigator sponsored study by Memorial Sloan Kettering Cancer Center (MSKCC), New York, USA was also initiated (NCT02609737). A total of 19 subjects (52% female) with heavily treated NETs and an average age of 55 years (range: 22 to 73) were included in this study. Subjects received an administration of approximately 1 to 2 GBq of ^{177}Lu-OPS201 for dosimetry purposes. The cumulative radioactivity for the consecutive therapeutic administrations was calculated based on the dosimetry results, ensuring that organ dose limits are not exceeded. The cumulative radioactivity was fractionated into two single administrations with a highest single radioactivity of 7.86 GBq and a highest cumulative radioactivity of 16.65 GBq. The administered compound contains up to 100 µg peptide (based on information from July 2016).

Seven subjects received two therapeutic cycles of ^{177}Lu-OPS201 with cumulative activities ranging from 13.28 to 16.65 GBq and the other subjects received only one therapeutic cycle with cumulative activities ranging from 6.94 to 9.43 GBq. After the first cycle the subacute haematological toxicity was mild to moderate in 17 subjects (79%) and two subjects exhibited Grade 3 leukopenia that reversed to Grade 1 or Grade 0 before the second cycle. By contrast, four of seven subjects were noted to have Grade 4 haematological toxicities (four thrombocytopenia and one leukopenia) starting 4 to 6 weeks after the second cycle. These Grade 4 toxicities were long lasting and resolved to Grade 2 or lower in 16 to 26 weeks after the last treatment cycle; none of these subjects demonstrated fever, infection, bleeding, or renal toxicity. The mean relative bone marrow absorbed dose (image-based method) was 0.077 Gy/GBq (range: 0.049 to 0.11) and the individual bone marrow absorbed doses ranged

from 1.3 Gy to 1.5 Gy in subjects who showed severe thrombocytopenia whereas it was below 1 Gy in the other subjects.

Following these safety events, the study was put on clinical hold and restarted following a protocol amendment that included lower radioactivity of ^{177}Lu-OPS201 in each cycle and a lower limit of permitted exposure to the bone marrow (1 Gy).

The median tumour absorbed dose in this study was about 7.2 Gy/GBq. Preliminary efficacy results indicate that one subject had a CR (5%), six had a partial response (PR) (32%), nine had SD (47%) and three had disease progression (16%). Among the seven subjects who received the two therapeutic cycles (13.28 GBq to 16.65 GBq), one subject had a CR (14%), three had a PR (43%), two had SD (29%) and one had disease progression (14%).

1.5 Rationale for the Study

In preclinical studies the high potential of ^{177}Lu-OPS201 as therapeutic agent for PRRT against GEP NETs has been demonstrated. In a preliminary study under compassionate use it was shown that these results are reflected in clinical examples.[43]

Other NETs beside GEP NET also express sstr2 (the target of ^{177}Lu-OPS201) thus providing scientific rationale for the inclusion of patients with NET tumours. Indeed, in the academic pilot study, which is described in Section 1.3.5, a patient with lung NET had been included who presented with a PR after treatment with ^{177}Lu-OPS201. Furthermore, since NET is a rare disease, enlargement of the population to more subtypes of this disease will facilitate recruitment for this study.

To make this treatment available to NET patients, systematic assessments are required for marketing approval. The first milestone is the demonstration of the safety and tolerability of the treatment, which is the classical endpoint of a phase I trial. In radiopharmaceutical studies this safety assessment also includes dosimetry studies to evaluate the radioactive exposure of organs. For PRRT the dose-limiting organ is usually the kidney with a safety limit of 23 Gy.

Since a single administration of ^{177}Lu-OPS201 would only carry a burden for the patient without the benefit of a complete PRRT treatment, it was decided to expand the study to a phase I/II trial with three cycles of ^{177}Lu-OPS201 treatment with an implemented radioactivity escalation step (in case the bone marrow and kidney dose do not exceed 1.5 Gy and 23 Gy, respectively). This provides not only the possibility to evaluate the safety and tolerability of a whole PRRT treatment with ^{177}Lu-OPS201, but also first information about the efficacy of the treatment. To create sufficient data for the set-up of a phase II/III trial, based on the phase I/II results, a study population of up to 55 subjects with histologically confirmed diagnosis of GEP and lung NETs and pheochromocytoma and paraganglioma is planned.

1.6 Justification of Dose

In a joint practical guidance, the International Atomic Energy Agency (IAEA), the European Association of Nuclear Medicine (EANM), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) describe the performance of PRRT in NETs as a very practical orientation.[35]

For the agonistic SSAs ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-TOC they suggest an applied radioactivity of 5.55 GBq to 7.4 GBq per cycle and a total of three to five cycles with a time interval between the cycles of 6 to 12 weeks.[35]

For this phase I/II study the planned radioactivity escalation ranges are in these limits. The original starting radioactivity chosen for this study was three cycles of 5.5 GBq of ^{177}Lu-OPS201. However, after preliminary results from an investigator-initiated trial (IIT) (refer to Appendix 5: Safety Information Letter), this radioactivity is now reduced to 4.5 GBq (target radioactivity 4.5 GBq±10%), resulting in a maximal targeted cumulative administered

radioactivity of 13.5 GBq fractionated into three administrations. This is in line with the pilot trial from Wild et al, [31] where the mean bone marrow dose was 0.1 Gy/GBq, and a cumulative radioactivity of 13.7 GBq with a bone marrow dose of 1.3 Gy did not lead to high grade haematotoxicity. A lower dose was not chosen to prevent under-treatment of patients. The international limit of the maximum bone marrow dose for nonmyeloablative therapeutic administrations is 2 Gy. In the referenced IIT, Grade 3 and higher haematotoxicity has been seen above bone marrow doses of 1.3 Gy and 0.9 Gy depending on the method of bone marrow dosimetry, which were based on blood and image analysis or blood analysis only. In the Wild et al [31] trial, Grade 3 thrombocytopenia was seen in one patient with a bone marrow dose of 1.5 Gy, calculated by a dosimetry method based on blood analysis only. Results of bone marrow dosimetry are variable and depend on the methodology used. Compared to methods taking into account blood and image analysis, methods based on blood analysis seem to underestimate the bone marrow dose.[44] In this study a method based on blood and image analysis will be used and the maximum bone marrow dose will be reduced to 1.5 Gy. The cumulative organ doses of kidney (maximum cumulative kidney dose is 23 Gy) and bone marrow are monitored in an ongoing manner. If a previous cumulative dose indicates that the organ limits will be exceeded with the next cycle, the radioactivity of the next cycle can be reduced or the cycle can be delayed.

In Part B of this study both the radioactivity and the peptide mass dose will be escalated. The planned radioactivity escalation can be reduced or increased to three cycles of up to 7.4 GBq (target injected radioactivity of 7.4 GBq±10%) ^{177}Lu-OPS201, depending on the safety data from Part A and ongoing evaluation of Part B.

Based on clinical experience, the practical guidance proposes peptide mass doses of 100 µg to 200 µg and an upper limit of 250 µg for ^{177}Lu-labelled agonists. However, this limit was not explained.

In the preliminary therapeutic study under compassionate use performed at the University Hospital in Freiburg, a peptide dose of 105±35 µg was applied.[43]

CCI [redacted] Peptide mass doses of 300 µg, 700 µg and 1300 µg (target mass dose±15%) will thus be evaluated in this study. The lowest peptide mass dose (300 µg) is higher than the dose of ≤100 µg used in the Wild 2014 study. [43]

Subject safety will be monitored by a safety review committee (SRC) in Part A and a data review board (DRB) in Part B (see Section 3.8).

1.7 Risk-benefit Assessment

As many radiopharmaceuticals are excreted rapidly in the urine, the absorbed dose to the wall of the urinary bladder is often large compared with the absorbed dose to other organs and tissues exposed to the same study dose [45]. In the urinary bladder wall and liver, the estimated absorbed doses (8.2 and 10.9 Gy, respectively) at the anticipated highest cumulative administered activity (3x7.4=22.2 GBq) are far lower than the radiation dose limit thresholds in the published literature (35 Gy for liver and 60 Gy for urinary bladder wall) [46].

Another factor that may potentially affect the development of haematological toxicity is radiation exposure to the spleen. As the spleen is part of the immune system, it can produce

blood cells and act as a major reservoir for red, white blood cells and platelets [47, 48, 49]. It is reported to be the organ that receives the highest mean absorbed dose of all organs during PRRT [50, 51], partly because of the presence of somatostatin receptors on lymphocytes [52, 53]. A dose dependent relationship may exist between the total absorbed dose to the spleen and the blood cell count [54]. In the spleen, the estimated absorbed dose is 66.6 Gy at the anticipated highest administered activity (3x7.4=22.2 GBq). However, there are no known radiation dose limits described in the literature.

Another potential risk is toxicity to other organs expressing somatostatin receptors (sstr2), such as the pituitary gland and pancreas as these organs are also potentially targeted by PRRT [55, 56, 57]. Therefore, it is not unlikely that patients treated with PRRT maybe are at risk of developing hormone disturbances or deficiencies during their follow-up period. To monitor any adverse effect on organs expressing sstr2, specific markers will be measured at each cycle during the study. For example, specific markers of the function of the hypothalamic-pituitary-adrenal axis, thyroid stimulating hormone (TSH), cortisol and IGF-1 will be measured at baseline, on Day 1 of each cycle and Day 2 of the first cycle and at the end of the core trial. Blood glucose will also be monitored.

All the other organs show less uptake with specific absorbed doses around 0.1 Gy/GBq and thus do not present any risk of overexposure compared to the radiation dose limit thresholds in the published literature [43]. The exception is the ovaries, where the radiation dose limit is 2 to 3 Gy (over this limit, there is a risk of permanent sterilisation). With a specific absorbed dose of 0.1 Gy/GBq, absorbed doses of about 2.2 Gy could be reached at the highest administered activity (22.2 GBq).

For Part A, every subject enrolled in this study must meet the inclusion criteria of having histologically confirmed diagnosis of unresectable NET and progressive disease (PD) according to the Response Evaluation Criteria In Solid Tumours (RECIST; v1.1 – see Appendix 2). PRRT is an effective therapy for patients with inoperable or metastasised NETs; conditions that are very common for this type of cancer due to the typically late diagnosis.[7, 8] Even in heavily pretreated patients with GEP NET, PRRT with ^{177}Lu-labelled sstr2 agonists have achieved remarkable response rates, and combined with kidney protective agents, the side effects of this therapy are few and mild.[58, 59]

For Part B, since the data became available that increasing peptide mass might be beneficial by improving the lesion to background radioactivity level, the study design was changed. Eight cohorts have been developed in a dose escalation methodology to assess both increasing peptide mass dose and increasing radioactivity. The design in two cohorts is a test-retest of increasing peptide at the second cycle to evaluate if receptor saturation is occurring. To ensure sstr2 lesions can be precisely evaluated with image dosimetry, a minimum of two sstr2 positive lesions are required for entry into the study. Hence the eligibility criteria are changed for Part B. This change is more stringent than the current eligibility criteria for Part A.

Preliminary data from the MSKCC study have been taken into account in the design of Study OPS-C-001. The new study investigates the same compound (^{177}Lu-OPS201), but with a higher peptide mass dose of 300 µg for Part A (compared to <100 µg in the MSKCC study). The planned cumulative radioactivity to be administered in Part A of the study is no more than 13.5 GBq, which is generally lower than the therapeutic cumulative radioactivity used in the MSKCC study. Furthermore, this cumulative radioactivity is fractionated into multiple administrations at lower radioactivity compared to the MSKCC study (3×4.5 GBq versus 2×of up >7 GBq). This approach is used since fractionation has been shown to contribute to better tolerability in radiotherapy.

Additional precautionary measures will include sequential recruitment in the first phase. An SRC will be held after full exposure of the first six subjects and before exposing a further nine subjects to the full radioactivity in Part A of the study (i.e. the seventh to fifteenth subjects can have up to two administrations but not more until the SRC on the first six subjects has been completed). The SRC will evaluate the safety data obtained until 8 weeks after the last administration of the sixth subject.

Prior to Part B, the SRC will review the safety and dosimetry data of all subjects included in Part A and a minimum of six completed subjects.

Detailed criteria, based on the percentage of subjects experiencing dose limiting toxicities (DLTs), have been carefully defined in the protocol in order to guide the radioactive dose selection for further enrolment in Part A and throughout Part B.

Haematology will be closely followed-up after each administration with daily monitoring during the first week and additional monitoring at 2 weeks after administration and every 2 weeks thereafter.

Participating subjects may be hospitalised until Day 2. The period of hospitalisation is left at the discretion of the investigator to allow the radioactivity levels to come back to safe levels for discharge and to protect medical personnel and relatives.

Maximum cumulative bone marrow exposure will be reduced to 1.5 Gy, a dose level used in the pilot study with no reported high grade haematotoxicity.[43]

Dosimetry will be measured up to 168 hours after each administration to describe the full bone marrow dose over the entire administration course.

The decision regarding the administered radioactivity at Visits 2 and 3 will be made only after careful consideration of the dosimetry and safety data following the preceding administration.

If the investigator is considering additional cycles for subjects, the benefit-risk need to be considered and discussed with the subjects with the approval of the sponsor.

In conclusion, the reduced radioactivity of 4.5 GBq together with the increased peptide mass in the proposed study compared to the MSKCC and the pilot[43] studies, are considered safe for administration to subjects, especially with the additional safety measures defined in the protocol (e.g. sequential recruitment and possible radioactivity reduction at Cycles 2 and 3).

Treatment benefit has been seen in the MSKCC and the pilot studies at even lower cumulative radioactivities than those planned, hence treatment benefit is also expected in this study. Taken together, an overall favourable benefit/risk ratio is expected for the subjects participating in Study OPS-C-001.

1.8 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. In addition, the study will adhere to all appropriate local regulatory requirements and relevant company policies.

Data will be collected by using an electronic case report form (eCRF) in compliance with Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to

subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

Almost all NETs express sstr2, making these tumours a potential target for treatment with PRRT. Therefore, the scientific rationale is to use sstr2 specific overexpression as a mean to target the delivery of the radioactivity to the tumour cells. This characteristic of sstr2 targeting shows promise as a personalised treatment approach such as theranostic combining imaging and therapy. The SSA peptide component (OPS200) is the targeting moiety of the compound with selective high affinity for sstr2 (OPS201 IC_{50}=0.70 nM and ^{177}Lu-OPS201 dissociation constant (K_d=0.072 nM) and antagonistic behaviour, thus no signal transduction is expected by the binding of ^{177}Lu-OPS201 to sstr2.

^{177}Lu is the active moiety of the compound; it is a β minus emitting radionuclide, with a mean energy of 0.133 MeV and a mean penetration depth of 0.23 mm.[35] In addition to β-emission, ^{177}Lu has gamma rays which allow performing SPECT images and consequently dosimetry. Hence, the compound ^{177}Lu-OPS201 may offer a treatment option beyond standard of care for NETs where there are still unmet clinical and therapeutic needs (see Section 1.3.2.2).

The purpose of the phase I of the study is to evaluate the safety and tolerability of the compound ^{177}Lu-OPS201 in previously treated subjects with unresectable GEP NETs, Lung NETs and malignant, unresectable pheochromocytoma or paraganglioma as well as to recommend a treatment schedule for the phase II; i.e. recommended cumulative radioactivity and fractionation, dosing interval and peptide mass dose.

2.2 Study Objectives

The primary objective of the study is to assess the safety and tolerability of PRRT with ^{177}Lu-OPS201 administered in three cycles in subjects with sstr2 positive NETs (including phaechromocytomas and paragangliomas).

The secondary objectives of the study are as follows:

- to evaluate the optimal radioactivity and peptide mass dose to be used in future studies;
- to characterise ^{177}Lu-OPS201 whole body biodistribution and 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 RECIST v1.1 status;
- to evaluate the influence of ^{177}Lu-OPS201 PRRT on the subject's quality of life.

The exploratory objectives of the study are as follows:

CCI

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

CCI

CCI

[redacted]

2.3 Study Hypotheses

(1) ^{177}Lu-OPS201 will be sufficiently safe to permit further clinical investigation when administered in previously treated subjects with unresectable GEP NETs, lung NETs and malignant, unresectable pheochromocytoma or paraganglioma.

(2) Increase of peptide mass doses leads to improved tumour to background ratio for ^{177}Lu-OPS201 administration, with a possible positive impact on the safety profile with an increasing tumour to bone marrow ratio.

3 STUDY DESIGN

3.1 General Design and Study Schema

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.

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 six 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; see Section 3.1.5) of ^{177}Lu-OPS201 at 8-week intervals (+2 weeks, or up to +4 weeks in case of AEs which have not adequately recovered (see Section 4.6)).

Subject safety and dose escalation (before initiating Part B) will be evaluated by an SRC in Part A and a DRB (Part B) (see Section 3.8 and Appendix 3).

The overall study design is shown in Figure 11, Figure 12 (Part A) and Figure 13 (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 scan (baseline for RECIST v1.1 evaluation) will be performed and a screening SRS will also be performed (unless already performed within 6 months prior to Visit 1 Day 1). Eligibility read for SRS and CT/MRI scans 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 End of Core Trial (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 tests 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 scan 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

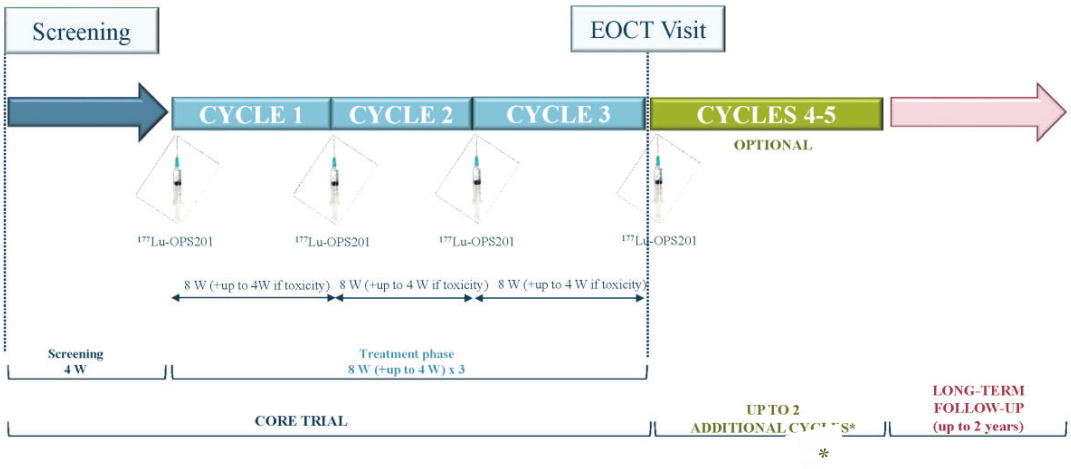
Visit 1: On Visit 1 Day 1, subjects will receive the first administration of ^{177}Lu-OPS201 followed by safety and extended dosimetry evaluations over 8 days, with additional laboratory safety tests repeated at Day 15 (±2 days). At Week 4 (Day 29±5 days), Week 6 (Day 42±5 days) (i.e. Follow-up Visit 1) and at 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 tests 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 tests 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 (see Section 3.1.5) 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 11 Overview of Study Design for Part A and Part B and Post Study Follow-up



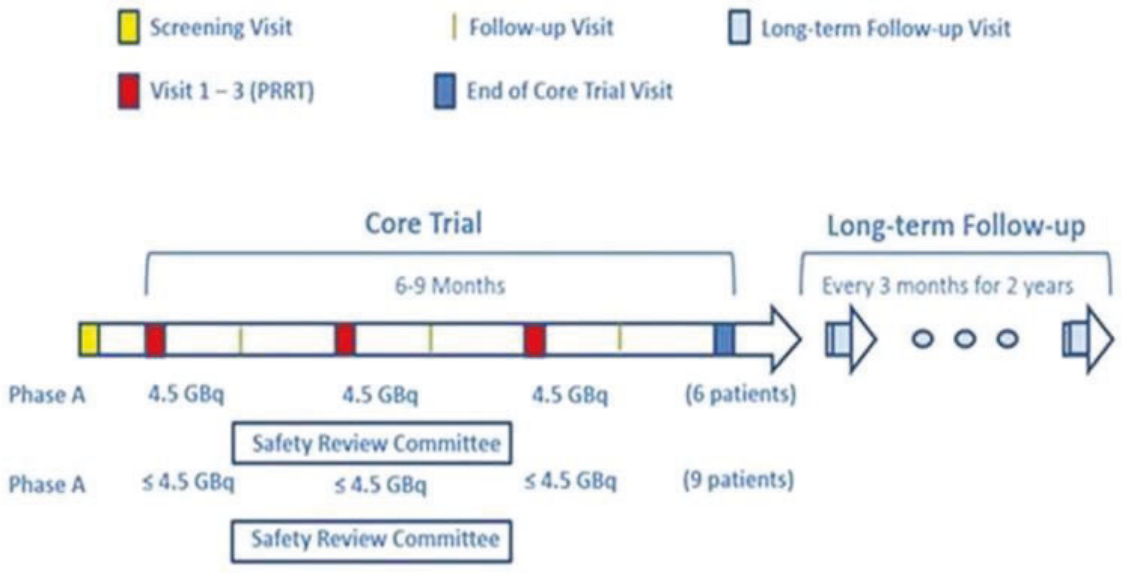
EOCT=end of core trial; W=weeks. *only for Part B

3.1.1 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 12 shows the study design for Part A.

Figure 12 Study Design - Part A



3.1.2 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 13.

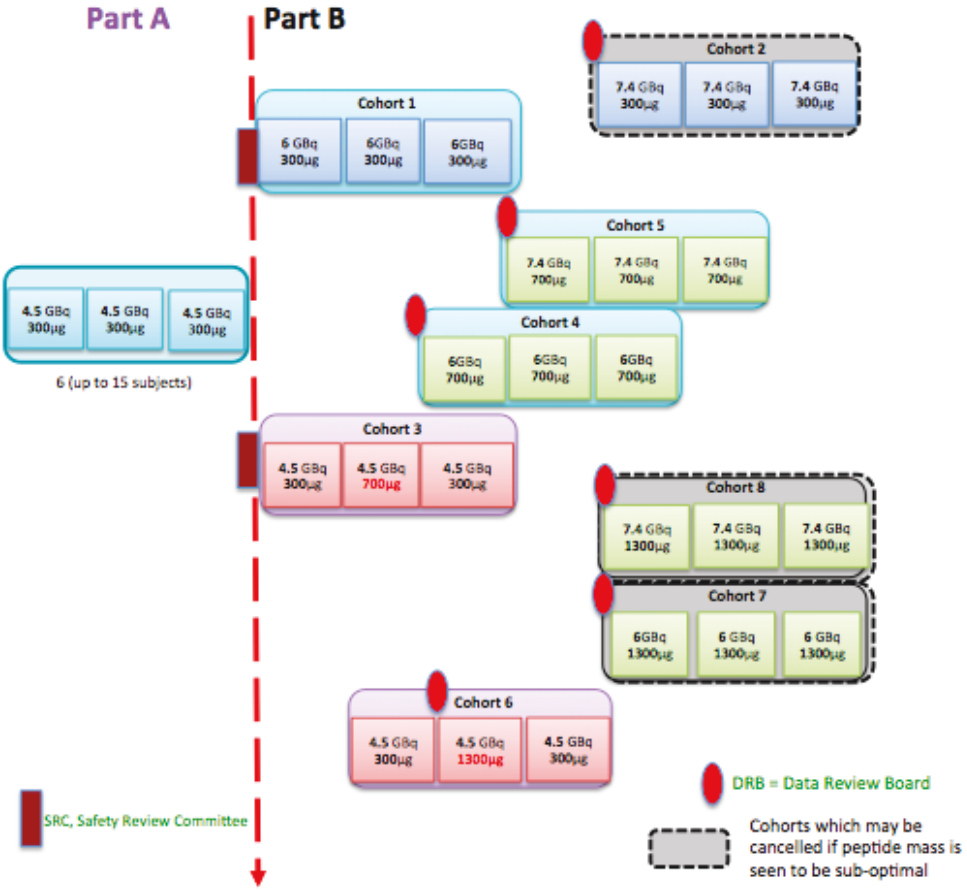
Part B will encompass radioactivity and peptide mass dose escalation as well as intra-individual peptide mass dose evaluation. It consists of up to eight cohorts. In each cohort, each subject will receive three cycles of the defined radioactivity and peptide mass dose of ^{177}Lu-OPS201

(see Section 6.2, Table 11). 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 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 6.4.2 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 (see Section 3.3). 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 13 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).

3.1.3 Justification for Part B Design

In animal experiments, no saturation of the sstr2 was observed when higher peptide mass doses were administered in a xenograft mouse model.[39] Nevertheless, the effect of the increasing peptide mass dose and the peptide mass at which lesion receptor saturation occurs in humans is unknown. The extrapolation from animal experiments may be limited by the fact that, in these

xenografts, receptor density was relatively high in comparison to normal distribution of receptors in the mouse.

Receptor saturation by the peptide is predicated on:

(a) the number of receptors in nontumoural tissue (physiological expression) and

(b) tumour burden and related sstr2 density (total receptor burden).

Regardless of tumour type, the higher the receptor burden the more peptide maybe required before saturation occurs. It is therefore important that the peptide masses being studied in this protocol are evaluated for sstr2 saturation. Hence Cohorts 3 and 6 will evaluate the peptide mass and specifically if receptor saturation has occurred, starting with 300 µg for Cycle 1, then increasing to 700 µg and 1300 µg respectively for Cycle 2 before repeating the 300 µg dosing for Cycle 3 (see Figure 13). Thus, the tumour-to-background dose ratio, and the tumour-to-bone-marrow dose ratio, using imaging dosimetry, can be evaluated in the same subjects. In these cohorts, administering 4.5 GBq/cycle, which was shown to be tolerated in Part A of the study, will allow comparison of intra-subject variability of the uptake due only to the peptide mass. It also allows Cohort 3 to start in parallel to Cohort 1 which is the next logical increase in dosing at 300 µg (6 GBq per cycle) following Part A.

The other cohorts in Part B will be initiated in a staggered manner after gaining experience with previous cohorts, thereby allowing safer investigation at higher radioactivity and/or higher peptide mass dose. If tumour sstr2 saturation is observed, then the lower peptide dose will be confirmed. Therefore, Cohorts 7 and 8 will be cancelled if the peptide saturation is seen in Cohorts 3 and/or 6. Similarly, Cohort 2 may be cancelled if a peptide mass dose range of 700 µg to 1300 µg is found to be optimal.

Subject numbers

Cohorts 3 and 6 will require 8 subjects to ensure there is sufficient power to demonstrate any tumour sstr2 saturation. Therefore 10 subjects will be enrolled to obtain a minimum of 8 completed subjects. All remaining cohorts (1, 2, 4, 5, 7 and 8) will enrol three to five subjects to obtain a minimum of three completed subjects per cohort.

Hence, it is anticipated that 10 subjects will be enrolled in Cohorts 3 and 6, and five subjects will be enrolled in Cohort 1, so the end-point can be achieved in these initial three cohorts rapidly (total of 25). To maintain the subject numbers to a maximum of 40 in Part B, if all remaining cohorts are utilised (total of five), each will have three subjects enrolled (total of 15).

Change in eligibility criteria for Part B

To ensure sufficient precision for the imaging dosimetry (specifically in Cohorts 3 and 6, but also for the whole study), eligibility will require a minimum of two lesions ≥20 mm in diameter. Tumour dosimetry should be performed on tumour lesions identified by the imaging core laboratory and on no more than five lesions (maximum two per organ, size ≥20 mm diameter, accessible for dosimetry). Furthermore, this ensures the modelling is based on a minimal total receptor burden.

Infusion rate

The i.v. infusion of ^{177}Lu-OPS201, should be at a rate of 10 mL/h over 120 minutes (see Section 6.2.1).

Investigators are advised that prophylaxis may be considered if the patient is thought to be at increased risk of infusion-related reactions as per the site's standard of care (see also 6.3.3 and Section 6.3.4). Appropriate treatment should be administered should an infusion-related reaction occur including somatostatin analogues. The administered radioactivity and mass dose follows the escalation scheme (see Section 6.2).

3.1.4 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 the investigator's judgment), 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 performed 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; please refer to Section 8.1.4.1.

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.

The schedule of assessments is provided in a flow chart (see Section 5.1) and is listed in Section 5.2. Unless otherwise specified, all assessments will be performed by the investigator or accredited study personnel.

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

3.1.5 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 EW except for exploratory biomarkers CCI [redacted]. 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 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.
  - organ absorbed doses did not exceed 1.5 Gy in bone marrow (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.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Safety Endpoints and Evaluations

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.

3.2.2 Secondary Endpoints and Evaluations

3.2.2.1 Biodistribution and Radioactive Pharmacokinetics of the Radiopharmaceutical Endpoints

- Maximal uptake (%) at the target lesions;
- Maximal uptake (%) in discernible organs and blood;
- AUC of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs, target lesions and blood;
- Terminal half-life of radioactivity concentrations of the radiopharmaceutical in blood.

3.2.2.2 Radiation Dosimetry Endpoints

- Organs receiving the highest absorbed dose;
- Specific absorbed dose to the target lesion (Gy/GBq);
- Specific absorbed dose per organ (Gy/GBq);
- Cumulative absorbed organ doses (Gy).

3.2.2.3 OPS201 Pharmacokinetics Endpoints

- If OPS201 levels are measurable in plasma and urine, 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), cumulative amount of unchanged drug excreted into the urine (Ae), renal clearance of the drug from plasma (CL_R) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of OPS201 and on the individual urine concentrations.

CCI [redacted]

3.2.2.4 Secondary Efficacy Endpoints

- Objective tumour response based on RECIST v1.1 (CT/MRI scan) by calculating best overall response (BOR), overall response rate (ORR) and disease control rate (DCR);
- PFS based on RECIST v1.1.

3.2.2.5 Influence of ^{177}Lu-OPS201 PRRT on the Quality of Life of the Subjects

- Quality of Life Questionnaire ((QLQ)-C30; GI.NET21) change from baseline to EOCT.

3.3 Exploratory Endpoints

CCI

3.4 Randomisation and Blinding

This is a nonrandomised, open label study. All eligible subjects will be assigned active study medication according to the radioactivity/peptide mass dose escalation plan. Independent readers will evaluate SPECT/CT Imaging and will be blinded to the radioactivity and peptide mass dose, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical examination findings.

Independent readers are specialised radiologists and/or nuclear medicine physicians who are experienced in reading SPECT/CT scans. To minimise inter- and intra-reader variability in results, the readers will be specifically trained for this protocol. See the Imaging Review Charter.

3.5 Maintenance of Randomisation and Blinding

This is a nonrandomised, open-label study.

3.6 Study Treatments and Dosage

The study treatment is manufactured and supplied to the clinical site as follows:

- clinical sites located in North America: from a central contract manufacturing organisation (Sofie Co., dba Sofie, 110 Clyde road, Somerset, NJ 08873, USA);

- clinical sites located in Europe: from a local radiopharmacy or from a central contract manufacturing organisation (Sofie Co., dba Sofie, 110 Clyde road, Somerset, NJ 08873, USA);
- clinical sites located in Australia: from a local radiopharmacy or from a central radiopharmacy (Brett and Peter Pty Ltd, located at Australian Radiopharmacy Group, 19 Prime Street, Thomastown, 3074, Victoria, Australia).

The study treatment will be supplied in a type 1 borosilicate glass vial sealed with a chlorobutyl stopper and aluminium seal, within a secondary shielding container, and is shipped inside Type A package for transporting radioactive materials when relevant. The study treatment will be labelled according to good manufacturing practice (GMP) and any applicable local laws/regulations.

The investigator's representative will receive:

- a Certificate of Analysis for each treatment which reflect the product release statement;
- Material Data Safety Sheet;
- packaging order.

Each label will be designed in accordance with Appendix 13 of the European Union (EU)-GMP and in accordance with specific local requirements if any.

For Part A the study treatment is a 20 mL solution for injection with OPS201 peptide mass dose of 300 µg with applied radioactivity of 4.5 GBq ^{177}Lu-OPS201 at the intended time and date of administration.

For Part B, the study treatment is a ready-to-inject 20 mL solution with OPS201 peptide mass dose nominally of either 300, 700 or 1300 µg and applied radioactivity dose of 4.5 GBq to 7.4 GBq ^{177}Lu-OPS201 at the intended time and date of administration.

The investigator or designee will only dispense the study treatment to subjects included in this study. Each subject will be given the study treatment carrying his/her number.

A more detailed description of administration procedures is given in Section 6.2.

3.7 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 will last 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. 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 (see Section 3.1.4).

3.8 Safety Review Committee (Part A) and Data Review Board (Part B)

The SRC will be composed of all investigators, who have treated at least one subject in the respective cohort with study medication, a dosimetry expert evaluating the dosimetry data of the study, an independent haematology 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 phases:

Part A (15 subjects)

Initially, six subjects will be treated in Part A. Each subject will receive three 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 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 in Part A to the entire number of planned administrations. Safety and dosimetry data from the first six subjects (data obtained up to 8 weeks after the last administration for each subject) will be evaluated during this SRC.

Dose limiting toxicity definition: 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 subjects, the remaining nine subjects will continue at the same radioactivity level.
- If DLTs occur in >33% of subjects, 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 three to two.

After treatment completion of the sixth subject (Part A), the SRC will decide, based on the safety and dosimetry data from Part A, if a radioactivity escalation is applicable in Part B.

The decision must be unanimous among the SRC members. The IRB/ECs will be notified of the radioactivity dose decision by the SRC.

Part B (up to 40 subjects)

The DRB will consist of a team of "permanent" decision makers (the core team), including selected principal investigators and Ipsen personnel. All final decisions will be made by the core team. The number of DRB meetings may change as needed and the DRB 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 the meeting can be conducted via email exchange or two conference calls with split attendees. A DRB charter will be developed with further details. Ad hoc DRBs can be convened at any time during the trial. See Appendix 3 for the details of the review required by the DRB.

Dose escalation (peptide mass dose and radioactivity, see Figure 13) will primarily be decided based on the clinical and safety data of the subjects.

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

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

If DLTs occur in >33% of subjects in the cohort, the next cohort will not be initiated.

- If DLTs occur in ≤33% 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 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 organ (1.5 Gy in BM and 23 Gy in kidney), the next cohort will be initiated as planned.

Each dose escalation (both peptide mass and radioactivity) will be carefully evaluated by the DRB. As safety and dosimetry information becomes available in other cohorts, this data will be used to evaluate the on-going cohorts and the subjects' dosing within the cohorts.

The DRB can make a recommendation as to the radioactivity dosing for the next cohort. This could include continuing the current cohort to complete five subjects for review. Alternatively, if any cohort dose (peptide or radioactivity) is closed down, with agreement from the DRB, the

next lowest dose may have three more subjects entered to confirm this is the maximum tolerated dose.

Based on the overall safety results, the DRB can also decide to start earlier or delay cohorts depending on the information available. Notification will be given to the principal investigators if this is to occur, with the rationale, as well as to the IRB/EC.

3.9 Source Data Recorded on the Case Report Form

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

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

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

Definition for source data and source documents are given below:

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

Imaging data for all subjects will be recorded electronically on digital media. These data and print-outs will be considered as source.

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

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

(1) written informed consent;

(2) subjects of either gender, aged ≥18 years;

(3) women of childbearing potential (not surgically sterile or less than 2 years postmenopausal) must use a medically accepted method of contraception and must agree to continue use of this method for the duration of the study and for 6 months after the last dose. Acceptable methods of contraception include abstinence, or double contraception: steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method (intrauterine device, condom, etc.);

(4) male subjects must use a medically accepted method of contraception and must agree to continue the use of this method for the duration of the study and for 6 months after the last radioactivity administration;

(5) Karnofsky performance score ≥60;

(6) life expectancy of at least 6 months;

(7) histologically confirmed diagnosis of:

- unresectable GEP NET (Grade I and Grade II according to WHO classification (2010, see Appendix 1), functioning and nonfunctioning);
- unresectable "typical lung carcinoid" or "atypical lung carcinoid" are acceptable (with the exception of Large Cell Bronchial Neuroendocrine Neoplasms and Small Cell Lung Cancers) [60];
- malignant, unresectable pheochromocytoma or paraganglioma;
  - subjects, who have histologically confirmed NET, but no clear localisation of their primary tumour, can be included;

(8) documentation of PD based on RECIST v1.1 under prior antitumour therapy within 6 months of Visit 1 Day 1 (although the progression might have occurred more than 6 months before Visit 1 Day1). Subjects should not have received further antitumour therapy once disease progression is documented. All images should be sent to the imaging core laboratory;

(9) in countries where sunitinib or everolimus are marketed, subjects with GEP NET and lung NET will be progressive under this prior antitumour treatment for the respective indication. Subjects not suitable for everolimus/sunitinib therapy according to a tumour board decision (or comparable local practice) may also be enrolled into the study. Subjects having everolimus/sunitinib therapy should have a wash-out phase of ≥4 weeks before the first treatment;

(10) measurable disease based on RECIST v1.1;

(11) **For Part A**: Confirmed presence of sstr on technically evaluable tumour lesions documented by a positive SRS*. If this has not been performed within 6 months of Visit 1 Day 1, then it must be repeated during screening.

* presence of at least one lesion that is ≥20 mm in the longest dimension (as measured on correlative CT or MRI scan) and with a maximum standardised uptake value (SUV_{max}) of ≥2 × the SUV_{mean} of the liver background on ^{68}Ga-PET imaging or a score of "3" or "4" according to the Krenning scale on SPECT imaging.

For Part B: Confirmed presence of sstr on technically evaluable tumour lesions documented by a positive SRS*. If this has not been performed within 6 months of Visit 1 Day 1, then it must be repeated during screening.

* presence of at least two lesions that are ≥20 mm in the longest dimension (as measured on correlative CT or MRI scan) and with an SUV_{max} of ≥2× the SUV_{mean} of the liver background on ^{68}Ga-PET imaging or a score of "3" or "4" according to the Krenning scale on SPECT imaging.

(12) calculated glomerular filtration rate (GFR) ≥55 mL/min;

(13) blood test results as follows:

- leukocytes: $\geq 4*10^9$/L;
- erythrocytes: $\geq 3.5*10^{12}$/L;
- platelets: $\geq 100*10^9$/L;

- albumin: >30 g/L;
- alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase: ≤5 times ULN;
- bilirubin: ≤2 times ULN (2×1.1 mg/dL).

4.2 Exclusion Criteria

Subjects will not be included in the study if the subject:

(1) known hypersensitivity to ^{177}Lu, DOTA, JR11 or to any of the excipients of ^{177}Lu-OPS201;

(2) Any previous PRRT;

(3) diagnosis of thymic NET;

(4) presence of active infection at screening, or history of serious infection within the previous 6 weeks;

(5) administration of any other investigational medicinal product (IMP) within 60 days prior to entry (Visit 1 Day 1);

(6) prior or planned administration of a therapeutic radiopharmaceutical within 8 half-lives of the radionuclide including any time during the current study;

(7) any extensive radiotherapy ≤3 months before first IRPP administration;

(8) chemotherapy ≤3 months before first IRPP administration;

(9) **for Part B:** Nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study as assessed by the investigator;

(10a) pregnant or breast-feeding women. A pregnancy serum test will be performed at the start of the study for all female subjects of childbearing potential (i.e. not surgically sterile or up to 2 years postmenopausal);

(11) any uncontrolled significant medical, psychiatric or surgical condition (active infection (including subject with known hepatitis B or hepatitis C and subjects with known human immunodeficiency virus (HIV) positive), unstable angina pectoris, cardiac arrhythmia, poorly controlled hypertension, poorly controlled diabetes mellitus (glycated haemoglobin (HbA1c) ≥9%), uncontrolled congestive heart disease, etc.) or laboratory findings that, in the opinion of the investigator, might jeopardise the subject's safety or that would limit compliance with the objectives and assessments of the study. Note: the subject should be able to tolerate high volume load.

(12) current history of any malignancy other than NET within 5 years of enrolment except for fully-resected non-melanoma skin cancer or cervical cancer in situ;

(13) any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.

4.3 Rationale for Inclusion/Exclusion Criteria

Eligibility criteria define subjects who fulfil the conditions for ^{177}Lu-OPS201 therapy. Subjects with neuroendocrine tumours (Grade I and Grade II), including phaeochromocytomas and paragangliomas will constitute the population in this study. A documented presence of sstr2 is a prerequisite to ensure that the subject may benefit from the sstr2 targeted treatment with ^{177}Lu-OPS201. Only PD is considered at this early stage of the IRPP development, as it is common practice in oncology drug development.

Importantly, some criteria are added to mitigate:

- risks known with PRRT treatment, especially haematological and renal side effects; of note, an exclusion criterion was added for Part B to avoid conditions that may put subjects at high risk of renal toxicity;
- risk of exposing pregnant women to radiations;
- other risks related to the subject's current clinical status including co-morbidities and concomitant treatments that are not compatible with the study treatment or study procedures, or which could significantly interfere with data analysis and interpretation;
- for Part B, more stringent requirements on the lesion burden to ensure sufficient receptor burden on target lesions.

4.4 Recruitment

It is intended that potential subjects for this study will be identified from patients currently attending or being referred to the study centres for the diagnosis and treatment of NETs, including phaeochromocytomas and paragangliomas. 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).

4.5 Subject Participation Card

A study participation card will be provided to each subject on the study. The card will indicate that they are participating in a clinical trial, and give the name and contact details of the sponsor and the investigator/study site. The subject will be asked to retain this card while they are participating in the trial and show it to any other medical practitioners they consult during this time. They will be advised to contact the investigator/study site if there are any questions.

4.6 Stopping Rules, Discontinuation and Withdrawal Criteria and Procedures

4.6.1 Withdrawal Criteria

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 subject from the treatment or the study for any of the following reasons:

- Safety Reason/AE: 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 nonserious AEs regardless of relation to study medication.
- Disease Progression: The investigator documents disease progression (based on RECIST v1.1 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 noncompliance, 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 eCRF.

- Lost to Follow-up: The subject stopped coming for visits, and study personnel were unable to contact the subject.

In the event of pregnancy, the subject 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 subject 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 as described in Section 6.4, 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 and reported in the eCRF.

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

Withdrawn subjects 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.

4.6.2 Withdrawal Criteria for Optional Biobanking

Subjects participating to the optional research biobanking program have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which the sample is kept). If a subject wishes to withdraw his consent for biobanking and the samples are still at the investigator site or at Central Laboratory at this time, the investigator must inform the study monitor in writing of the subject's decision and destroy the samples. The study monitor will forward confirmation of the destruction to Biomarker/Biobanking study monitor.

If the samples are at the sponsor's repository (biobanking vendor), the investigator must inform directly Ipsen using the e-mail address, CCI [redacted], mentioning only the subject study ID in this e-mail. Ipsen will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the withdrawal, which will be forwarded to the investigator. Analyses conducted before the withdrawal will not be affected.

4.6.3 Study or Site Termination

Study or site termination will occur if the sponsor or their representatives, investigator, or CA officials discover conditions during the study that indicate that the study or site involvement should be terminated. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study;
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the study drug;
- Failure of the investigator(s) to comply with pertinent clinical trial regulations;
- Submission of knowingly false information from the research facility to the sponsor, Clinical Monitor, or CA;
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in accordance with applicable local regulations.

5 STUDY PROCEDURES

NOTE: the study medication (OPS201), and all the biosamples (including blood, urine and biopsy material taken on study) are all radioactive and all due precautions are to be taken to protect subjects, study staff, persons preparing, transporting or analysing materials and members of the public.

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.

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 7 for Part A and in Table 8 for Part B.

Table 7 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
Tumour markers	x	x[e]						x	x[e]						x	x	x
[redacted]																	
Pituitary markers		x[e]	x													x	
Urinalysis	x	x[e]				x	x	x	x[e]					x	x	x	x
Radioactive PK and dosimetry [h][i]		x	x	x	x	x			x	x	x	x	x				
[redacted]																	
[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.

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 8 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]		EOCT/EW Visit during the Core Trial (±5 days) [b]	EOAC/EW Visit during additional cycles [b] [v]	LTFU Visits (up to 2 years)
	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)			
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
Tumour markers	x	x[e]						x		x[e]						x		x	x	x
CCI																				
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][i]		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 [redacted]																				
OPS201 PK[l] [m]		x	x	x																
CCI [redacted]																				
CCI [redacted]																				
CCI [redacted]																				
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.

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).

n a tumour biopsy will be taken at screening following confirmation of subject eligibility (if an archived biopsy is not available from up to 6 months before baseline, Visit 1 Day 1) and at Follow-up Visit 2 (i.e. at the same time point as RECIST assessment after Visit 2 or at disease progression, if this occurs earlier). If no biopsy material has been collected at Visit 1 Cycle 1, no further biopsy should not be performed for the purpose of the study (as it could not be compared to a baseline).

CCI [redacted]

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 CCI [redacted]

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.

The total volume of blood drawn for all evaluations throughout this study is up to 306.0 mL in Part A and up to 563.5 mL in Part B across 23 visits (Part A) or 41 visits (Part B) and will not exceed 77.5 mL at any one visit and 158.5 mL within 1 month (see Section 5.3 and Table 9). The total amount will be greater for subjects participating in Part B, which includes OPS201 PK, blood for CCI [redacted] in all sites (5 mL of whole blood for serum) and CCI [redacted] The total volume of blood for biobanking is 33 mL, which is an optional assessment.

5.2 Study Visits

The schedule of visits and main procedures at each visit are summarised in the study flowchart (see Section 3.1). If the time buffers of the visits are utilised, later visits must be shifted accordingly.

5.2.1 Screening Visit

Week -4 to -1

Depending on the SRS, a hospitalisation of up to 2 days may be necessary.

- written informed consent
  - study informed consent and optional informed consent for biobanking
- clinical assessments
  - demographic details
  - medical history and concurrent (baseline) conditions
  - concomitant and prior medications (taken up to 28 days before the Screening Visit)
  - physical examination
  - height
  - vital signs and 12-lead ECG
  - clinical laboratory tests (biochemistry, haematology, and urinalysis)
  - circulating tumour marker (blood)
  - serum β-human chorionic gonadotropin (HCG) pregnancy test for women of childbearing potential (not surgically sterile or 2 years postmenopausal)
  - review of inclusion and exclusion criteria.
  - performance status.
- CT/MRI (not older than 1 month on the first day of the Screening Visit)
- sstr scan (unless already performed within 6 months of Visit 1 Day 1)
- CCI [redacted]

5.2.2 Visit 1

During Visit 1, patient may be hospitalised on Day 1 for 24 hours and up to Day 8. The duration of the hospital stay is left at the discretion of the investigator and will depend on the individual subject and the regulatory requirements at the study site. Later assessments can be performed on an outpatient basis.

All postdosing time points are defined from stop of infusion (0).

5.2.2.1 Visit 1, Day 1 (Week 0)

Safety assessments (predosing results must be checked before ^{177}Lu-OPS201 administration; these can be performed 1 day before administration)

- physical examination
- weight
- vital signs and 12-lead ECG
- performance status
- clinical laboratory tests (biochemistry, haematology, pituitary marker and urinalysis)
- serum β-HCG or urine pregnancy test for women of childbearing potential (not surgically sterile or 2 years postmenopausal)
- AEs/concomitant medications
- 24 hour ECG (Holter) (to start before amino acid infusion).

Efficacy assessments

- Quality of Life Questionnaire (QLQ-C30; GI.NET21)
- tumour markers.

CCI

[redacted]

Administration of ^{177}Lu-OPS201

See Section 6.2.

Safety assessments (postdosing)

- vital signs (stop of infusion, 0.5 hours ±5 minutes, 1 hour ±10 minutes, 4 hours ±10 minutes)
- AEs/Concomitant medications

Dosimetric measurements

- blood sampling (2 mL) before and at stop of infusion (0) and 5 minutes±1 minute, 0.5 hours±3 minutes, 1 hour±5 minutes, 4 hours±10 minutes postinfusion
- whole body imaging at 4 hours±10 minutes
- SPECT/CT imaging (Part B only) at 4 hours±10 minutes
- urine collection 0 to 6 hours and 6 to 24 hours postinfusion (Part A), 0 (start of the infusion) to 4 hours, 4 to 24 hours postinfusion at visit 1 only (0 (start of the infusion) to 4 hours only for US and Canada sites) (Part B)

OPS201 PK assessments (Part B only)

- blood samples for assessment of OPS201 plasma levels will be collected at the following time points at visit 1 only: before the infusion (baseline), at the end of the infusion (0), 5 minutes±1 minute, 30 minutes±3 minutes, 60 minutes±5 minutes and

4 hours±10 minutes, 6 hours±30 minutes, and 8 hours±30 minutes after the administration of ^{177}Lu-OPS201.

- urine collection for assessment of OPS201 urine levels will be collected at the following time periods at visit 1 only: from 0 (start of the infusion) to 4 and 4 to 24 after the start of infusion (0 (start of the infusion) to 4 hours only for US and Canada sites).

CCI [redacted]

Efficacy assessments

- Survival

5.2.2.2 Visit 1, Day 2

Safety assessments (at 24±1 hour)

- clinical laboratory tests (biochemistry, haematology, pituitary marker)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 24±1 hour)

- blood sampling at 24±1 hours
- whole body imaging
- SPECT/CT imaging
- urine collection 24 to 48 hours postinfusion at visit 1 only (not applicable for US and Canada sites)

OPS201 PK assessments (Part B only)

- blood samples for assessment of OPS201 plasma levels will be collected 24 hours (±1 hour) after the administration of ^{177}Lu-OPS201 at visit 1 only.
- urine collection for assessment of OPS201 urine levels will be collected from 24 to 48 hours after the start of infusion at visit 1 only (not applicable for US and Canada sites).

CCI [redacted]

5.2.2.3 Visit 1, Day 3

Safety assessments (at 48 hours±1 hour)

- clinical laboratory tests (biochemistry, haematology)
- Vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 48 hours±1 hour)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only)
- urine collection 24 to 48 hours at visit 1 only (continued) (not applicable for US and Canada sites).

OPS201 PK assessments (Part B only)

- blood samples for assessment of OPS201 plasma levels will be collected 48 hours (±1 hour) after the administration of ^{177}Lu-OPS201 at visit 1 only.
- urine collection for assessment of OPS201 urine levels will be collected 24 to 48 hours at visit 1 only (continued) (not applicable for US and Canada sites).

CCI [redacted]

5.2.2.4 Visit 1, Day 4 (-Day 5)

Safety assessments (at 72 to 96 hours)

- laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 72 to 96 hours)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

CCI [redacted]

5.2.2.5 Visit 1, Day 7 (-Day 8)

Safety assessments (at 144 to 168 hours postinfusion)

- clinical laboratory tests (biochemistry, haematology and urinalysis)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 144 to 168 hours postinfusion)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

CCI [redacted]

5.2.2.6 Visit 1, Day 15 (±2 Days)

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)
- vital signs
- AEs/concomitant medications.

5.2.3 Follow-up Visit 1

Follow-up Visit 1 should be Week 4 (Day 29±5) and Week 6 (Day 42±5) if no previous visit window was extended. At Week 6, only safety assessments such as clinical laboratory tests (biochemistry, haematology and urinalysis) will be performed.

5.2.3.1 Week 4 (Day 29±5)

Safety assessments

- physical examination
- clinical laboratory tests (biochemistry, haematology, and urinalysis)
- vital signs and 12-lead ECG
- AEs/concomitant medications.

Efficacy assessments

- survival
- tumour markers.

CCI [redacted]

5.2.3.2 Week 6 (Day 42±5) - Part B only

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)

5.2.4 Visit 2

During Visit 2, patient may be hospitalised on Day 1 for 24 hours and up to Day 4. The duration of the hospital stay is left at the discretion of the investigator and will depend on the individual subject and the regulatory requirements at the study site. Later assessments may be performed on an outpatient basis.

5.2.4.1 Visit 2, Day 1 (Week 8 (+2 Weeks or Up to +4 Weeks in Case of AEs which have Not Adequately Recovered))

Safety assessments (predosing results must be checked before ^{177}Lu-OPS201 administration; can be performed one day before)

- physical examination
- weight
- vital signs and 12-lead ECG
- performance status
- clinical laboratory tests (biochemistry, haematology, and urinalysis)
- serum or urine pregnancy test for women of childbearing potential (not surgically sterile or 2 years postmenopausal).
- AEs/concomitant medications
- control of withdrawal from treatment criteria (see Section 6.4)
- 24-hour ECG (Holter) (to start before amino acid infusion).

Efficacy assessments

- survival
- quality of life questionnaire (QLQ-C30; GI.NET21)
- tumour markers
- CT/MRI (same method as in Screening Visit); +2 weeks or up to +4 weeks in case of AEs

CCI [redacted]

CCI [redacted]

Administration of ^{177}Lu-OPS201

See Section 6.2.

Safety assessments (postdosing)

- vital signs (stop of infusion, 30±5 minutes 60±10 minutes, 4 hours ±10 minutes)
- AEs/concomitant medications.

Dosimetric measurements

- blood sampling before and at stop of infusion at 60±5 minutes, 4 hours ±10 minutes
- whole body imaging at 4 hours ±10 minutes.
- SPECT/CT imaging (Part B only) at 4 hours ±10 minutes.

5.2.4.2 Visit 2, Day 2

Safety assessments at 24 hours ±1 hour

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements at 24 hours ±1 hour

- blood sampling
- whole body imaging
- SPECT/CT imaging.

5.2.4.3 Visit 2, Day 3

Safety assessments at 48 hours ±1 hour

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements at 48 hours ±1 hour

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

5.2.4.4 Visit 2, Day 4 (-Day 5)

Safety assessments

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 72 to 96 hours postinfusion)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

CCI [redacted]

5.2.4.5 Visit 2, Day 7 (-Day 8)

Safety assessments (at (144 to 168 hours postinfusion)

- clinical laboratory tests (biochemistry and haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 144 to 168 hours postinfusion)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

5.2.4.6 Visit 2, Day 15 (±2 Days)

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)
- vital signs
- AEs/concomitant medications.

5.2.5 Follow-up Visit 2

Follow-up Visit 2 should be Week 12 (Day 29±5) and Week 14 (Day 42±5) if no previous visit window was extended. At Week 14, only safety assessments such as clinical laboratory tests (biochemistry, haematology and urinalysis) will be performed.

5.2.5.1 Week 12 (Day 29±5)

Safety assessments

- physical examination
- clinical laboratory tests (biochemistry, haematology, and urinalysis)
- vital signs and 12-lead ECG
- AEs/concomitant medications.

Efficacy assessments

- survival
- tumour marker
- tumour biopsy taken at Follow-up Visit 2 or at disease progression. If no biopsy material has been collected at Visit 1 Cycle 1, no further biopsy should be performed for the purposes of the study (as it could not be compared to a baseline).

CCI [redacted]

5.2.5.2 Week 14 (Day 42±5) - Part B only

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)

5.2.6 Visit 3

During Visit 3, a patient may be hospitalised on Day 1 for 24 hours and up to Day 4. The duration of the hospital stay is left at the discretion of the investigator and will depend on the individual subject and the regulatory requirements at the study site. Later assessments may be performed on an outpatient basis.

5.2.6.1 Visit 3, Day 1 (Week 8 (+2 Weeks or Up to +4 Weeks in Case of AEs which have Not Adequately Recovered))

Visit 3, Day 1, should take place 8 weeks after Visit 2 (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered). This should be Week 16 (+2 weeks or up to +4 weeks in case of AEs which have not adequately recovered), otherwise Week 16 should be changed to the appropriate week number.

Safety assessments (predosing, results must be checked before ^{177}Lu-OPS201 administration; can be performed one day before)

- physical examination
- weight
- vital signs and 12-lead ECG
- performance status
- clinical laboratory tests (biochemistry, haematology, and urinalysis)
- serum or urine pregnancy test for women of childbearing potential (not surgically sterile or 2 years postmenopausal).
- AEs/concomitant medications
- control of withdrawal from treatment criteria (see Section 6.4)
- 24 hour ECG (Holter) (start before amino acid infusion).

Efficacy assessments

- survival
- quality of life questionnaire (QLQ-C30; GI.NET21)
- tumour markers
- CT/MRI (same method as in Screening Visit); +2 weeks or up to +4 weeks in case of AEs

Exploratory biomarkers

CCI [redacted]

Administration of ^{177}Lu-OPS201

See Section 6.2.

Safety assessments (postdosing)

- vital signs (stop of infusion, 30±5 minutes 60±10 minutes, 4 hours ±10 minutes
- AEs/concomitant medications.

Dosimetric measurements

- blood sampling before and at stop of infusion, 1 hour ±5 minutes, 4 hours ±10 minutes
- whole body imaging at 4 hours ±10 minutes
- SPECT/CT imaging (Part B only) at 4 hours ±10 minutes.

5.2.6.2 Visit 3, Day 2

Safety assessments at 24 hours ±1 hour

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements at 24 hours ±1 hour

- blood sampling
- whole body imaging
- SPECT/CT imaging.

5.2.6.3 Visit 3, Day 3

Safety assessments at 48 hours ±1 hour

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements at 48 hours ±1 hour

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

5.2.6.4 Visit 3, Day 4 (-Day 5)

Safety assessments (at 72 to 96 hours)

- clinical laboratory tests (biochemistry, haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 72 to 96 hours postinfusion)

- whole body imaging
- blood sampling
- SPECT/CT imaging (Part B only).

CCI [redacted]

5.2.6.5 Visit 3, Day 7 (-Day 8)

Safety assessments (at 144 to 168 hours postinfusion)

- clinical laboratory tests (biochemistry and haematology)
- vital signs
- AEs/concomitant medications.

Dosimetric measurements (at 144 to 168 hours postinfusion)

- blood sampling
- whole body imaging
- SPECT/CT imaging (Part B only).

5.2.6.6 Visit 3, Day 15 (±2 Days)

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)
- vital signs
- AEs/concomitant medications.

5.2.7 Follow-up Visit 3

Follow-up Visit 3 should be Week 20 (Day 29±5) and Week 22 (Day 42±5) if no previous visit window was extended. This visit should take place 4 weeks ±5 days after Visit 3. At Week 22, only safety assessments such as clinical laboratory tests (biochemistry, haematology and urinalysis) will be performed.

5.2.7.1 Week 20 (Day 29±5)

Safety assessments

- physical examination
- clinical laboratory tests (biochemistry, haematology and urinalysis)
- vital signs and 12-lead ECG
- AEs/concomitant medications.

Efficacy assessments

- survival
- tumour markers

CCI [redacted]

5.2.7.2 Week 22 (Day 42±5) - Part B only

Safety assessments

- clinical laboratory tests (biochemistry, haematology and urinalysis)

5.2.8 End of Core-trial Visit

The EOCT Visit should take place 8 weeks after Visit 3. This should be Week 24 (Day 1±5) if no previous visit window was extended. 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 (Part B only).

Safety assessments (at EOCT/EOAC Visit)

- vital signs and 12-lead ECG
- physical examination
- weight
- performance status
- clinical laboratory tests (biochemistry, haematology, pituitary markers and urinalysis)
- AEs/concomitant medications (see Section 8.1.4.1).

Efficacy assessments (at EOCT/EOAC Visit)

- CT/MRI (same method as in Screening Visit); ±5 days' window acceptable
- quality of life questionnaire (QLQ-C30; GI.NET21)
- survival

- tumour markers.

CCI

[redacted]

5.2.9 Long-term Follow-up Visits (1 to 8)

Long term follow-up visits will be carried out every 3 months for 2 years starting 12 weeks after the EOCT/EOAC/EW Visit (see Section 3.1.4). In the long-term follow-up phase, deviations (±2 weeks) from the time schedule are not recorded as significant deviations.

Tumour assessments will be assessed every 3 months (±2 weeks) until whichever occurs first: documented disease progression (radiological or clinical as per the investigator's judgment), 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 performed 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.

Efficacy assessments

- CT/MRI (same method as in Screening Visit); ±2 weeks' window allowable
- survival
- tumour markers.

Long-term safety assessment

- vital signs and 12-lead ECG
- physical examination
- laboratory tests (biochemistry, haematology, and urinalysis)
- AEs/concomitant medications (NET only) (see Section 8.1.4.1).

5.2.10 Early Withdrawal Visit

This visit will be performed if a subject withdraws from trial participation (treatment and any Follow-up procedures) and consents to this last visit. The assessments at this visit correspond to the EOCT/EOAC Visit.

If the study subject withdraws early from the trial, the EW Visit should be performed 8 weeks after the last administration study medication).

Safety assessments

- vital signs and 12-lead ECG
- physical examination
- weight
- performance status

- clinical laboratory tests (biochemistry, haematology, pituitary markers, specific renal safety biomarkers and urinalysis)
- AEs/concomitant medications (see Section 8.1.4.1)

Efficacy assessments

- CT/MRI (same method as in Screening Visit); ±5 days' window allowable
- survival
- quality of life questionnaire (QLQ-C30; GI.NET21)
- tumour markers.

CCI [redacted]

5.3 Laboratory Assessments

The total volume of blood to be collected from any subject during the core trial will be up to 306 mL (Part A) or up to 563.5 mL (Part B) across 23 visits (Part A) or 41 visits (Part B) and will not exceed 77.5 mL at any one visit and 152.5 mL within 1 month (see Table 6). The total amount will be greater for subjects participating in Part B, which includes OPS201 PK. The total volume of blood for biobanking is 33 mL, which is an optional assessment.

Table 9 Volume of Blood During the Core Trial

Test	Volume per Sample	Maximum number of Samples (Part A)	Maximum number of Samples (Part B)
Haematology	2 mL	23	42
Biochemistry	5 mL	23	42
Tumour markers	4 mL	8	8
Pituitary biomarkers	6 mL	3	3
Blood sampling for radiopharmaceutical PK	2 mL	26	42
OPS201 PK blood	2 mL	NA	10
CCI [redacted]			
TOTAL number of samples		**91**	**166**
TOTAL Volume		**306 mL**	**563.5 mL**

5.4 Functional Imaging: Somatostatin Receptor Scan

Functional imaging by SRS will be performed at the Screening Visit.

The selection of the peptide depends on the regulatory requirement in the specific country of this multinational trial and will be the responsibility of the investigator. A PET/CT scan with ^{68}Ga-labeled SSA is preferable.

The screening SRS will be performed within 1 month before Visit 1 Day 1. If a historic SRS is available, and not older than 6 months prior to Visit 1 Day 1, this scan can be used.

For Part A, the eligibility of subjects will require the presence of:

- At least one lesion that is ≥20 mm in the longest dimension (as measured on correlative CT or MRI);
- And with SUV_{max} ≥2× the SUV_{mean} of the liver background on ^{68}Ga-PET imaging, or a score of "3" or "4" according to the Krenning scale (see Table 10) on SPECT imaging.

For Part B the eligibility of subjects will require the presence of:

- At least two lesions that are ≥20 mm in the longest dimension (as measured on correlative CT or MRI);
- And with SUV_{max} ≥2× the SUVmean of the liver background on ^{68}Ga-PET imaging, or a score of "3" or "4" according to the Krenning scale (see Table 10) on SPECT imaging of the two identified lesions.

Table 10 Krenning Scale

Score	Uptake
0	No abnormality/no uptake
1	Faint uptake
2	Clear uptake in tumour but less than in liver
3	Uptake greater in tumour than liver
4	Uptake much greater in tumour than liver

6 TREATMENT OF SUBJECTS

6.1 Investigational Medicinal Product Preparation Storage and Accountability

6.1.1 Investigational Medicinal Product Storage and Security

All study material will be kept in a secure, restricted-access location and in accordance with applicable regulatory requirements, within the radiopharmacy of the Nuclear Medicine Department.

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

Despite precautions, if spillage or leakage should occur, then the site procedures must be implemented to protect the subject, staff and members of the public from radiation exposure. The subject should be moved from the area of the spillage or leakage while the area is decontaminated. Details of the spillage or leakage should be recorded (including how the incident happened, the time of the incident, an estimate (if possible) of the amount of substance lost) and the measures taken. In addition, the incident is to be reported in the same manner as an adverse event using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) Product Leakage and as appropriate PT Occupational exposure to radiation (if there is exposure to staff) and PT Exposure to radiation (if there is exposure to the subject or members of the public). Such "special situation" events should be reported to the sponsor in same timelines as an SAE (within 24 hours) using the Ipsen's SAE form, even if the event did not result in any AE. See Section 9.2.1 for additional scanning requirements in case of spillage (or interruption of infusion).

6.1.2 Investigational Medicinal Product Preparation

For production in radiopharmacies:

The hospital radiopharmacy will order the required ^{177}Lu, on demand, following the local procedures of the hospital.

OPS201 precursor for radiopharmaceutical preparation will be supplied in glass vials as an acetate salt powder. OPS201 precursor will be manufactured, handled and stored in accordance with Good Pharmacy Practice.

The hospital radiopharmacist will perform the radiolabelling of OPS201 precursor to obtain the radiolabelled study medication according to the radiolabelling procedure provided in a ^{177}Lu-OPS201 radiolabelling procedure manual (see IRPP dossier). Upon completion of radiopharmacy procedures, the study medication will be labelled according to GMP and any applicable local laws/regulations, and the radiopharmacist will hand over or ship the study medication to the investigator or a designated and suitably qualified deputy for administration. The radiolabelling, dispensing and quality control is described in the site specific IRPP manual for the ^{177}Lu-OPS201 Radiolabelling Procedure.

For production in central contract manufacturing organisation:

The IRPP will be supplied as a ready-to-use solution for injection.

6.1.3 Investigational Medicinal Product Accountability

The sponsor will supply to the trial site sufficient materials to conduct the study after receipt of all required documentation, including written approval from the IEC/IRB and Regulatory Authority, as appropriate.

At the end of the study, when applicable, any unused quantities of precursor for radiopharmaceutical preparation will be returned to the sponsor or will be locally eliminated according to all requirements for the destruction of radioactive materials. The return or elimination of any unused precursor will be documented appropriately.

The investigator is obliged to keep sufficient documentation of the delivery, use and destruction or return of unused, used or partially used packages of IRPP. The documentation must include dates, quantities, subject numbers, batch numbers or other identification number. The investigator may assign some or all of the investigator's duties for drug accountability to an appropriate radiopharmacist.

The investigator should maintain records that document adequately that the subjects were administered the doses specified in the protocol and reconcile all IRPP received for the trial. The local study monitor will be responsible for checking the drug accountability records maintained by the site during the monitoring visits.

The medication provided for this study is for use only as directed in the protocol. It is the investigator/Institution's responsibility to establish a system for handling study drug, so as to ensure that:

- Deliveries of IRPP are correctly received by a responsible person;
- Such deliveries are recorded;
- Study treatments are handled and stored safely and properly as stated on the label;
- Study drug is only dispensed to study subjects in accordance with the protocol; and
- Any unused study drug is destroyed locally or returned for destruction in liaison with the Clinical Research Associate (CRA).

Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock. Records of usage should include the identification of the

subject to whom the study treatment was dispensed, and the quantity and date of dispensing. The radioactivity should also be recorded before and after administration. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a radiopharmacist, and copies retained in the Radiopharmacy File. The return or destruction of unused drug will be conducted after written approval by the sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

6.2 Study Drugs Administered

Subjects will be treated with three cycles 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 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.

The study will be performed in two phases.

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 (see Section 3.8 for DLT rules).

Part B (up to 40 subjects)

Table 11 provides the specific radioactivity and peptide mass dose for each cohort in Part B.

Table 11 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

6.2.1 Dosage and Administration of Study Medication

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 (see also Section 6.3.3 and Section 6.3.4). 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.

To protect the kidneys, an amino acid solution is infused with ^{177}Lu-OPS201 (Section 6.3.2). The same venous access for IRPP and amino acid solution administration (see Section 6.3.2) will be used. Infusion should be done into the contra-lateral arm of the PK sampling.

The administered radioactivity and mass dose follow the escalation scheme (see Section 3 and Section 6.2).

Note: The rate of infusion can be adjusted based on recommendations from the DRB.

The same venous access for IRPP and amino acid solution administration (see Section 6.3.2) will be used. Infusion should be done into the contra-lateral arm of the PK sampling.

At any time, if infusion-related reactions are encountered, the infusion should be slowed or interrupted.

Radioactivity evaluation (Part A)

In Part A, a cumulative radioactivity of 13.5 GBq (4.5 GBq/cycle × three cycles) with a peptide mass dose of 300 µg will be evaluated.

Radioactivity and dose escalation (Part B)

See Table 11 for the peptide mass and radioactivity dosing per cohort. See Section 3.1.3 for the rationale of the cohorts and Section 3.8 for dose escalation.

Subjects who experience a significant toxicity and recover from the toxicity, may be allowed to continue to receive study treatment at a lower activity level, subject to review and approval by the sponsor. These subjects must be closely monitored for safety. Please refer to Section 6.4 for Delay of Administration and Withdrawal from Study Treatment.

6.3 Concomitant Medication/Therapy

6.3.1 Interruption of Somatostatin Analogue Therapy

Somatostatin analogue therapy for symptom control will be allowed before and during the course of the study. If a subject is undergoing therapeutic treatment with any SSA, it is possible to interrupt the therapy before the administration of ^{177}Lu-OPS201.

As a recommendation: if a subject is on a long-acting somatostatin analogue, such as Somatuline Autogel® or Sandostatin® LAR, a wash-out period of 28 days is recommended

before injection of the study drug. If a subject is on a short-acting somatostatin analogues, such as Sandostatin® a wash-out period of 24 hours is recommended before injection of the study drug. The decision on the interruption of SSA use is the responsibility of the investigator and must be documented.

The somatostatin analogue can be re-started 24 hours after the infusion of OPS201, but the same washout periods should be observed at every cycle of study treatment. Concomitant medications should be reviewed periodically as the symptoms associated with the NET might be reduced if the tumour comes under control.

For subjects with severe functional NET symptoms, the investigator is free to pursue SSA treatment as preclinical data (presented by Guillaume Nicolas et al. at the EANM congress 2015/Poster OP307) indicate that the binding of the antagonistic peptide ^{177}Lu-OPS201 is not impaired by the use of SSAs.

In order to determine whether or not the concurrent use of somatostatin analogues has an effect on the activity associated with OPS201, response rates amongst those subjects who receive concurrent somatostatin analogues will be compared to the response rates amongst those subjects whose somatostatin analogues are interrupted at the time of treatment.

6.3.2 Amino Acid Infusion: Renal Protection

It has been shown that the renal absorbed dose, which is the treatment-limiting factor of PRRT, can be effectively reduced by the concomitant administration of cationic amino acids. Based on the joint IAEA, EANM and SNMMI practical guidance on PRRT in NETs [35] a solution of 25 g lysine and 25 g arginine in 2 L saline is recommended to be infused concomitant to the PRRT administration over 4 hours, starting 30 to 60 minutes before the infusion of ^{177}Lu-OPS201. The infusion time can be extended to 6 hours in case of e.g. technical infusion problems, interruption of infusion due to AEs or subjects' intolerance of the high-volume load in a short time. The guidelines for the infusion of the amino acids should be followed as closely as possible, unless there is a contraindication. If the infusion is not complete after 4 hours, a long infusion line (2 m) can be used to continue the infusion while the whole-body scan and SPECT/CT scan are done (but note the long line can cause increased pressure and result in a slowing of the infusion rate which might require correction). The line should be made of PVC (Non-DEHP and free of Latex). The infusion of OPS201 must be complete when the long infusion line is inserted as the extra length of line would increase the amount of radioactive substance in the infusion line and so increase the radiation exposure to the public and to staff.

Centres experienced in PRRT treatment can use their established amino acid solution, if it is covered by the recommendations of the joint IAEA, EANM and SNMMI practical guidance on PRRT in NETs and agreed with the sponsor, or Ipsen amino acid solution (auxiliary medicinal product OPS301, depending on the availability at the study site). The exact formulation and source must be documented in the eCRF. OPS301 has been formulated in compliance with the established guidelines and like other similar products is acidic (pH5.5).

6.3.3 Antiemetic

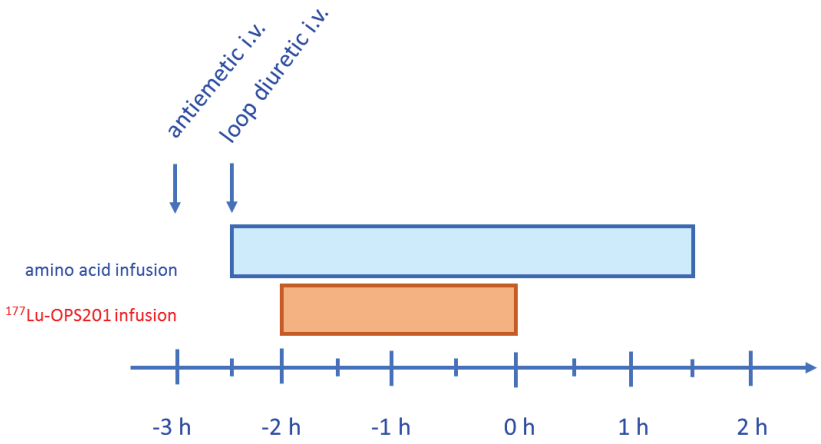
To counteract the known side effects of this amino acid infusion, such as nausea, 8 mg dexamethasone (antiemetic) and as-required ondansetron (8 mg i.v.) will be administered 15 to 30 minutes before the start of the amino acid infusion (unless there are contraindications for these drugs). From adoption of the protocol version (v6.0), investigators are advised, if required, to control symptoms it is allowed to use antiemetic regime as per site´s standard of care and to add extra antiemetic medication including short-term steroids (unless there are contraindications for these drugs). Any antiemetic drug administered to the subject must be documented in the eCRF.

6.3.4 Optional: Loop Diuretic

To facilitate the renal elimination of the radioactive peptide, 20 mg furosemide i.v. (loop diuretic) can be administered 30 to 60 minutes prior to the administration of the study medication. This is optional and can be decided by the investigator, but must be documented in the eCRF.

6.3.5 Administration Scheme

Figure 14 Administration Schedule for Study Treatment and Concomitant Medication



i.v.=intravenous.
0 h=end of infusion.
Antiemetic and loop diuretic are administered if required.
^{177}Lu-OPS201 infusion takes place over 120 minutes (see Section 6.2.1).

6.3.6 Prior and Further Concomitant Treatments

Subjects will be excluded from the study if they have received any other IRPP. Therapy given subsequently to study medication needs to be considered carefully: if radionuclide therapy is used, the prior radiation doses to the normal tissues need to be considered; and any therapy (such as chemotherapy or radionuclide therapy) should not be started until it is clear that the subject has recovered sufficiently from the adverse events associated with study medication.

During the study period other concomitant medications are permitted at the discretion of the investigator. With the exception of the therapeutic use of SSAs (see Section 6.3.1), NET-specific treatments are not allowed until the end of the core study. In case the investigator considers a NET-specific treatment is deemed necessary for the benefit and well-being of the subject, they should withdraw the subject from study treatment and perform the Withdrawal visit as specified in Section 5.

Vitamins, herbal preparations and other nutritional supplements are permitted during this study.

Prior medications (up to 28 days prior to the Screening Visit) and all medications (including herbal products) taken until the EOCT or EOAC Visit, whichever occurs last, must be recorded in the subject's eCRF. The only treatments recorded during the Long-term Follow-up period will be further antitumour treatments for NETs. The indication for each drug, generic name, administration form, strength, dose, frequency of dosing, route of administration, start date and, if applicable, stop date should also be recorded in the eCRF. All medications will be encoded according to the Anatomical Therapeutic Chemical/Defined Daily Dose Classification of the European Pharmaceutical Market Research Association.

6.4 Delay of Administration and Withdrawal from Treatment

6.4.1 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*109/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 criteria, see Appendix 4) and does not resolve within 4 weeks (resolved=toxicity Grade 2 or lower and is at the discretion of the investigator):
  - estimated GFR (eGFR) of <45 mL/min/1.73m^2;
  - liver function tests (total bilirubin and 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 AE 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 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 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.

6.4.2 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, see Appendix 4) 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 and must be discussed with and agreed by the sponsor. 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.

6.5 Treatment of Overdose

Accidental overdosing is highly unlikely as medication will be prepared individually for each subject by a qualified radiopharmacist. In the event of accidental overdosing of radio-labelled product, this may result in increased tissue exposure. The subject should be treated according to acceptable protocols by the investigator. This might include measures to increase excretion (e.g. hydration or diuretics) and preparation for the treatment of damage to critical organs such as the kidney and bone marrow (as kidney failure or myelodysplastic syndrome). There is no specific guidance for overdosing. All procedures must be in accordance with the local Radiation Protection guidelines.

Drug overdose is a reportable "Special Situation" and should be reported in the same format and within the same timelines as a SAE, even if it did not result in an AE.

Overdose is defined as any dose administration where >25% in excess of the correct radioactivity amount is administered whether or not associated with an AE.

For monitoring purposes, any case of overdose must be reported in the eCRF's Safety Section in an expedited manner.

If the pharmacy discovers that an overdose has or may have been administered, they should inform the Study investigator and Study Coordinator.

6.6 Post Study Treatments

Following completion of this study, all treatments and interventions will be at the investigator's discretion according to clinical practice and subjects' needs.

6.7 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. Subjects can be withdrawn from the study at any time if the investigator or the sponsor determines that the subject is not in compliance with the study protocol.

The investigator is obliged to keep sufficient documentation of the delivery, use and destruction or return of unused, used or partially used packages of IRPP. The investigator should maintain records that document adequately that the subjects were administered the doses specified in the protocol and reconcile all IRPP received for the trial.

Records of usage should include the identification of the subject to whom the study treatment was dispensed, the quantity and date of dispensing. Administration compliance will be assessed by the trained staff/nurse performing the injection. The radioactivity should also be recorded before and after administration. In case of incomplete injection of the IRPP, the residual volume left (or the residual radioactivity) in the syringe should be recorded in the eCRF. Any discrepancies must be accounted for on the appropriate forms.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Section 5.1.

7.1 Efficacy Endpoints and Evaluations

The efficacy endpoints are presented in Sections 3.2.2.4 and 3.3.1.

CCI [redacted]

The tumour volume assessment:

- Part A: sstr2 lesions are identified as having visible uptake of ^{177}Lu-IPN01072 on SPECT/CT. Only the lesions monitored in dosimetry are included.
- Part B: sstr2 lesions are identified by the prestudy sstr2 scan. The lesions that are identified on PET or SPECT by sstr2 scan as measured by CT/MRI scan will be the target lesions CCI [redacted]

[redacted]

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

Methods for assessing efficacy data is described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 15.1, and methods of analyses are discussed in Section 11.4.

7.2.1 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.

7.2.2 Quality of Life Questionnaire

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.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

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. Further details for AE reporting can be found in Section 8.1.2.3.

8.1.1 Definition of an Adverse Event

The definition of an AE below follows ICH GCP guidelines (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse Event (AE): 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.

By definition, for this study, 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.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

The severity of an event is captured in order to subcategorise events. Severity is not seriousness. A very severe event can be nonserious, and a serious event can be of a mild severity. For this study, the US NCI CTCAE v5.0 should be used for determining an event's severity.

All AEs (including SAEs) are to be accurately recorded on the AE page of the subject's eCRF. Each event will be graded for severity using the classifications of CTCAE v5.0 (see Appendix 4). For events not addressed in the CTCAE v5.0, 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; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL;
- Life-threatening (Grade 4) - Life-threatening consequences; urgent intervention indicated;
- Death (Grade 5) related to AE.

8.1.2.2 Causality Classification

The relationship of an AE to IRPP or OPS301 if applicable, 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 or OPS301 if applicable, 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 or OPS301 if applicable, administration.

Causal relationship of an AE with regards to both administration of IRPP and OPS301 (for subjects who received OPS301) should be recorded. The relationship of the study treatment to an AE will be determined by the investigator and subsequently reviewed by the sponsor.

8.1.2.3 Assessment of Expectedness

The reference safety document used in this trial is the Investigator Brochure (IB).

Expected conduct-related AEs: the use of an indwelling cannula for the purpose of blood sampling and administration of study drug may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the vessel wall. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to single vein punctures for blood sampling.

Subjects may also experience discomfort from lying beneath the camera, e.g. back pain.

Expected adverse reaction related to amino acid solution: nausea and vomiting are adverse reactions commonly reported with the use of cationic amino acid solutions as renal protection method.

Expected adverse drug reactions (ADRs): the definition below follows ICH GCP (see also ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Adverse drug reaction: in the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered as ADR. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Unexpected ADRs: The sponsor will assess all SAEs whether they are expected or unexpected. An unexpected ADR is defined as any adverse drug experience, the nature, specificity or severity of which is not consistent with the applicable product information (e.g. IB for an unapproved investigational product or Summary of Product Characteristics for an approved product). "Unexpected" as used in this definition refers to an adverse drug experience that has not been previously observed and included in the product information, rather than from the perspective of such experience not being anticipated from the pharmacological properties of the investigational product.

8.1.2.4 Laboratory Test Abnormalities

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

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

8.1.2.5 Abnormal Physical Examination Findings

All abnormalities in physical examinations are to be recorded as AEs. If an abnormal physical examination finding meets any of the criteria for an SAE, it must be reported on an SAE Form.

8.1.2.6 Other Investigation Abnormal Findings

All abnormal vital signs are to be recorded as AEs. Results of 12-lead ECG will be immediately analysed by a cardiologist or qualified investigator, and any clinically relevant findings are also to be recorded as AEs. ECG results will also be reviewed centrally. If an abnormal ECG, or vital sign finding meets any of the criteria for an SAE, it must be reported on an SAE Form.

8.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IMP and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this IMP.

AESIs for ^{177}Lu-OPS201 include events with a potential allergic or immunological mechanism which may require more frequent monitoring and/or supportive interventions. These AESIs are being closely monitored in the clinical studies with ^{177}Lu-OPS201. If the investigator has any questions regarding an AE being an infusion related reaction (IRR), the investigator should promptly contact the sponsor's clinical monitor or his/her designated representative. All AESIs will be assessed and reported as AEs on the AE page of the eCRF by the investigator and periodically evaluated by the sponsor.

The signs and symptoms of IRR may include:

- vasovagal reaction
- hypotension
- palpitations
- tachycardia
- sweating
- gastrointestinal (nausea or vomiting, metallic taste in mouth, right upper quadrant pain, abdominal cramps or bloating / diarrhoea)
- wheezing

8.1.4 Recording and Follow-up of Adverse Events

At every visit during the study period, the subject will be asked a nonleading question such as "Have you had any health problems since you were last asked/seen?" All AEs reported in response to questioning, as well as AEs reported spontaneously and occurring at any other time, will be recorded on the "Adverse Event" page(s) of the eCRF, regardless of causality.

If an AE fulfils any of the criteria for a SAE, both the AE pages of the eCRF and the SAE Form must be completed.

All abnormal laboratory results that are clinically significant and, abnormalities in physical examinations and vital signs are to be recorded as AEs. Results of 12-lead ECG will be immediately analysed by a cardiologist or qualified investigator, and any clinically relevant findings are also to be recorded as AEs. ECG results will also be reviewed centrally. If an abnormal laboratory (e.g. electrolytes disorders), physical examination, ECG, or vital sign finding meets any of the criteria for an SAE, it must be reported on an SAE Form.

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

For both serious and nonserious AEs, documentation must be supported by an entry in the subject'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 nonserious, investigator's opinion of the relationship to investigational drug, treatment required for the AE, action taken with IRPP or OPS301 if applicable, and information regarding resolution/outcome.

8.1.4.1 Reporting of Adverse Events

Any AE/SAE occurring during the study, from informed consent up to 6 months after last study drug administration, must be reported to the sponsor.

Up to 6 months after the last study drug administration, all AEs/SAEs will be collected unless NET therapies are started, then only AEs/SAEs considered by the investigator to be 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.

8.1.5 Reporting of 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)).

- Hospitalisation is defined as any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit. (NB: only the inpatient admission not related to IRRP admission and in link with reportable SAE per protocol definition will be recorded in eCRF).
- Prolongation of hospitalisation is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE

or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting.

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

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

Actions and reporting obligations in case of SAEs

All SAEs (as defined above), regardless of treatment group or of suspected relationship to IRPP or OPS301 if applicable, must be reported immediately. Therefore, all pertinent questions in the eCRF's Safety Report Section must be answered and the form signed. This triggers immediate notification of the sponsor through an email alert. The SAEs should be reported to the sponsor within 24 hours of awareness by completing an Ipsen SAE paper form included in the site folder and sending it to the sponsor by e-mail (preferably) or fax.

For SAE reporting:

Email: PPD
Fax:

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

- study number
- site number
- subject number
- AE
- IRPP (^{177}Lu-OPS201) information with administration date/dose/radioactivity
- OPS301 information with administration date (if applicable)
- investigator's name and contact details.

If the fall back solution was used for reporting an SAE, an Ipsen SAE form must be filled with all available details (as many as possible) within 24 hours and sent to Ipsen within 24 hours. The event data must still be entered by the site into the eCRF as soon as technical problems have been solved to ensure that all events are consistently entered into the study database.

Any other relevant documents such as anonymised copies of hospital records may also be attached, if available, taking care to redact the subject's name and address and to add the subject's study number on each page.

In the event of subject death, a detailed description of the cause of death should be provided. If available, autopsy reports, with the subject's name and address redacted and the subject's study number written on every page, should also be sent to the sponsor using the contact routes above, as soon as they become available. Any additional information which becomes known to the investigator should be provided in a follow-up report to the numbers above.

Notification to the IEC/IRB: the sponsor will be responsible for ensuring the notification to the IEC/IRB of all relevant events (e.g. SAEs and suspected unexpected serious adverse reactions (SUSARs)) according to all applicable regulations.

Notification of the regulatory authorities: the sponsor will ensure all relevant events (e.g. SAEs, SUSARs) are reported to the regulatory authorities according to all applicable regulations.

Exposure during pregnancy or lactation, see Section 8.1.7

8.1.6 Suspected Unexpected Serious Adverse Reactions

SUSARs are serious adverse events that are not consistent in nature, specificity or severity with the reference safety information in the approved IB, and that the investigator and/or sponsor identifies as related to IRPP or OPS301 if applicable.

8.1.7 Pregnancy

Pregnancy and lactation are exclusion criteria for this clinical study. If pregnancy occurs during the course of the study, the subject must be withdrawn from study and closely followed-up during the entire course of the pregnancy and postpartum period.

If a site becomes aware of a subject's (or their partner's) pregnancy or of exposure via breastmilk, the sponsor must be notified without delay by entering pertinent data in the Safety Section of the eCRF.

The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. For pregnancies, parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Offspring should be followed up for at least 8 weeks after delivery. If the expected due date is after the end of the study period, the sponsor will assume responsibility for follow-up through the due date/8 weeks post-partum, and for the regulatory reporting of any pertinent follow-up information.

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

8.1.8 Deaths

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 8.1.2.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these three AE options:

- death not otherwise specified (NOS),
- disease progression NOS,
- multi-organ failure,
- sudden death.

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

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IRPP (see Section 4.6.1).

If the IRPP is discontinued due to an SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.5). In case of suspected or confirmed COVID-19 infection, the IRPP administration may be temporarily discontinued depending on the subject's

clinical presentation. In some cases, the investigator may request a subject be retested before the IRPP administration is resumed.

In all cases, the investigator must ensure the subject receives appropriate medical follow-up (see Section 4.6.1).

8.1.10 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the sponsor immediately. If a subject experiences an SAE associated to a pharmaceutical technical complaint, it must be specified in an SAE form. The same reporting timelines as for SAEs apply.

8.1.11 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The sponsor will ensure that processes are in place for submission of reports of SUSARs and other important safety information occurring during the study to the CA, IECs and other investigators concerned by the IRPP. Reporting will be done in accordance with the applicable regulatory requirements.

8.1.12 Risk-benefit Management

With the exception of the two studies previously described, this is the first clinical trial with ^{177}Lu-OPS201 conducted by Ipsen. Thus, this study is subject to the precautions detailed in "Guideline on strategies to Identify and Mitigate Risks for First-in-human Clinical Trials with IMPs" (EMEA/CHMP/SWP/28367/07). In particular, i.v. administration of a peptide may conceivably result in a hypersensitivity reaction. Adequate resources, including an intensive care unit, must be available at the site to handle acute reactions, including anaphylactic shock. Emergency equipment will be available in the nuclear medicine department and anywhere else in the hospital where the study will take place.

8.2 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.

8.2.1 Haematology

Samples will be tested for 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 (+ optional Visits 4/5) (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.

8.2.2 Blood Biochemistry

Samples will be tested for 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) (preferably isotope dilution mass spectrometry (IDMS)-traceable MDRD) formula [61].

Biochemistry will be measured at the Screening Visit, at Visits 1 to 3 (+ optional Visits 4/5) (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.

8.2.3 Urinalysis

Sample will be tested for 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 (+ optional Visits 4/5), 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.

8.2.4 Pregnancy Test

Prior to each PRRT cycle (Screening Visit and Visits 1 to 3 (+ optional Visits 4/5), 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.

8.2.5 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 will not be analysed 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.

8.3 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.

8.4 Height and Weight

Subject height will be measured at the Screening Visit, while weight will be assessed predose at Visits 1 to 3 (+ optional Visits 4/5) and at the EOCT/EOAC/EW Visit. Body surface area will be determined with the Mosteller formula.

8.5 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 (+ optional Visits 4/5) (predose, postinfusion: at stop of infusion (0), 30±5 minutes, 60±10 minutes, 4 hours ±10 minutes, 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), Day 15, Follow-up Visits, the EOCT/EOAC/EW Visit and the visits in the 2-year long-term follow-up period.

8.6 Electrocardiography

A 12-lead ECG will be performed at the Screening Visit, predose at Visits 1 to 3 (+ optional Visits 4/5), 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 – see Figure 14), 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 at the visits in the 2-year long-term follow-up period. Results will be provided to the site and retained as source data.

8.7 Performance Status

The performance status of the subjects will be defined by the Karnofsky scoring and assessed at the Screening Visit, predose at Visits 1 to 3 (+ 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.

8.8 Subject Demographics

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

8.9 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.

8.10 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.

9 ASSESSMENTS OF PHARMACOKINETICS

Timing of sample collections must be accurately recorded in the eCRF.

9.1 Pharmacokinetics of the Radiopharmaceutical

9.1.1 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 duration for measuring the radioactivity concentration must be recorded. Any issues associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for sample collection, processing and handling will be provided in a "Dosimetry Operation Manual".

9.1.2 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 periods:

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 and the total urine volume for each collection interval must be recorded. All problems associated with sample collection or processing should be reported to the sponsor's monitor.

Complete instructions for urine collection, processing and handling will be provided in a "Dosimetry Operation Manual".

9.1.3 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 point of the sample collection and the time point and the duration for measuring the radioactivity concentration must be recorded. Complete instructions will be provided in a DOM.

9.2 Nuclear Medicine Imaging for Dosimetry

Radioactive assessments in blood and urine are described in Section 9.1.

9.2.1 Whole Body Scan

To determine the biokinetics, whole body scans (planar scintigraphy) will be obtained after bladder emptying 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.

In case of misadministration (such as spillage or interruption of the infusion for AEs), a whole body scan (but not SPECT) will be required shortly after the end of infusion and before the first bladder emptying.

Details on the procedures will be given in a separate DOM.

9.2.2 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.

Details on the procedures will be given in a separate DOM.

9.3 Pharmacokinetics of the OPS201

9.3.1 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.

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.

Complete instructions for sample collection, processing, handling and shipment will be provided in the laboratory manual.

9.3.2 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.

Complete instructions for urine collection, processing, handling and shipment will be provided in the laboratory manual.

9.3.3 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. Residual plasma and urine used for OPS201 PK analysis may also be used for exploratory analysis. CCI Plasma and urine samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long-term stability, reproducibility).

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10 EXPLORATORY BIOMARKERS AND BIOBANKING

10.1 Exploratory Biomarkers

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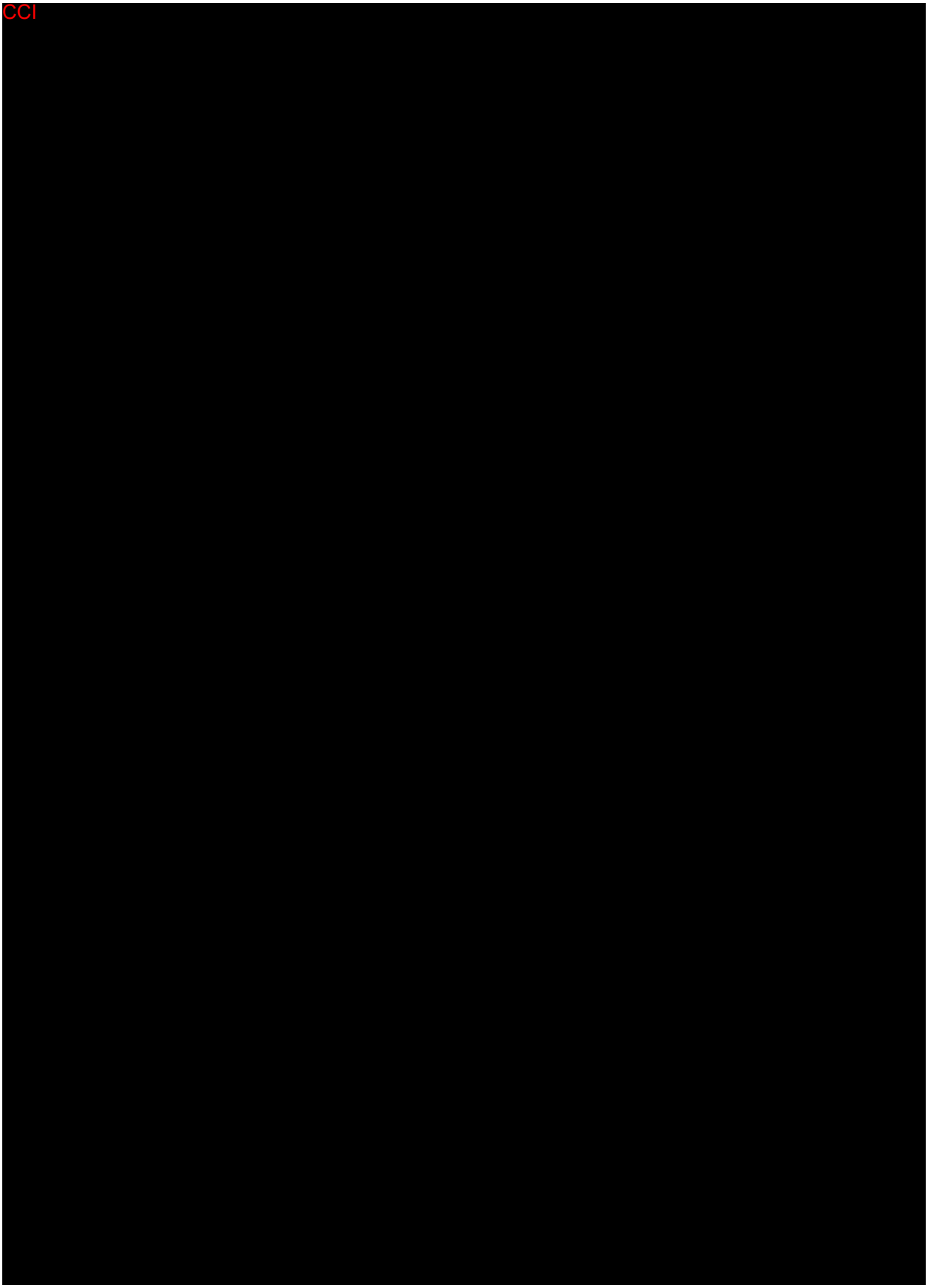

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11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study are documented in a statistical analysis plan (SAP), v1.0 Final which is dated and completed on 09 March 2017 (revisions may be made to this to incorporate changes made to methodology of Part B in the protocol v6.0 and up). The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (v9.2 or higher)

11.1 Analyses Populations

Subjects will be assigned to each analysis set prior to the statistical analysis. The following population will be used during statistical analyses:

- **Screened Subjects Set**: 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).
- **Safety Analysis Set**: all subjects who received study medication.
- **Intent-to-Treat Set (ITT)**: all subjects in the Eligible Subjects Set who received study medication.
- **Per-Protocol Set (PP)**: 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.
- **Intent-To-Treat Dosimetry Analysis Set (ITT-DAS)**: all subjects in the ITT Set for whom at least one complete set of dosimetry imaging and dosimetry blood sample measurements is available.
- **Per-Protocol Dosimetry Analysis Set (PP-DAS)**: all subjects in the ITT-DAS for whom no major protocol violations occurred affecting dosimetry variables.
- **Radiopharmaceutical Pharmacokinetic Set**: For Part A and Part B, 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.

- **OPS201 Pharmacokinetic Set (for Part B only):** all subjects 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 AUC).

11.1.1 Populations Analysed

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.

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

11.1.2 Reasons for Exclusion from the Analyses

Any major protocol deviation (see Section 13.1.2 for definition) will be described and its impact on inclusion in each analysis population (PP, safety and PK populations) for any subject will be specified. The final list of protocol deviations impacting the safety, ITT and PP populations will be reviewed prior to database lock. The list may be updated, up to the point of database lock, to include any additional major protocol deviations impacting inclusion in the PP population.

11.2 Sample Size Determination

It is anticipated that a total of up to 55 subjects will be recruited, up to 15 subjects in Part A and up to 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 may be recruited as replacements to ensure an adequate sample size in the "per protocol set" for safety evaluation. Subjects with noninterpretable 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.

11.3 Significance Testing and Estimations

As this is a descriptive safety and tolerability/efficacy study, no formal statistical testing will be carried out.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by external contract research organisations (CROs), managed by the sponsor's Biometry Department.

Details of the statistical analysis are specified in the SAP.

The statistical analyses will be conducted using SAS (v9.2 or later).

Primarily, all variables will be analysed descriptively, as follows:

- Mean, standard deviation, median and range for continuous variables
- Median, range and frequency distribution for discrete (ordinal) variables
- Frequency distribution for nominal variables.

Secondarily, the variables descriptive statistics will be presented by study part. If appropriate, results for total, Part A+B will be presented. In the event of dose escalation, study Parts A and B will be compared using nonparametric tests. The test results will be interpreted in an exploratory manner. 95% confidence intervals will be estimated as appropriate.

Data collected during the Long-term Follow-up will be analysed by means of a survival analysis (Kaplan-Meier method) with the respective plots and descriptive summaries.

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum) and frequency counts of demographic and baseline data (medical history, concomitant disease, predosing AEs and ongoing medical history, prior medications and therapies, baseline symptoms, etc.) will be presented for the ITT, PP, safety and PK populations.

11.4.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the ITT, PP, safety and PK populations will be tabulated. The reasons for subject exclusions from each of the populations will be listed and tabulated. In addition, the numbers of subjects who received study treatment, discontinued and completed at each of the study periods (e.g. active follow-up period, survival follow-up period) will be tabulated. Primary reasons for discontinuation of study treatment will be listed and tabulated.

11.4.3 Efficacy Data

Descriptive summaries will be performed for the efficacy data and the quality of life questionnaire data for each time point as applicable. Preliminary antitumour activity will be measured by calculating BOR, ORR and DCR. For each response category, the number and associated percentage of subjects will be presented by study part, and by cohort (applicable for Part B) and overall. Time to PFS will also be estimated using the Kaplan-Meier method to calculate the median (associated 95% confidence interval) by study part, by cohort (applicable for Part B) and overall. The summaries will be based on the ITT and PP populations. For imaging efficacy endpoints, these will be summarised separately for the central and the investigator assessment.

11.4.4 Biodistribution and Radioactive Pharmacokinetics of the Radiopharmaceutical

The following biodistribution (i.e. organ PK) parameters will be evaluated:

- maximal uptake (%) at the target lesion,
- maximal uptake (%) in discernible organs and blood,
- AUC of ^{177}Lu-OPS201 in discernible thoracic and abdominal organs, target lesion and blood,
- terminal half-life of radioactivity concentrations of the radiopharmaceutical in blood.

Data analysis and all biodistribution parameters will be further described in the SAP.

11.4.5 Pharmacokinetic Data

The PK analysis of OPS201 will be performed under the responsibility of the sponsor's Clinical PK department.

Analysis of PK data by a noncompartmental approach will be documented in a separate SAP. Individual plasma and urine concentrations of OPS201 will be listed and summarised by time points using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean and geometric coefficient of variation assuming lognormally distributed data). Linear and semi-logarithmic plots of individual and mean plasma concentration-time profiles as well as spaghetti plots will be reported.

Any suspicious concentration will be investigated and kept in the PK analysis if possible. All excluded concentrations will be justified in the report.

If OPS201 levels are measurable in plasma and urine, PK parameters of OPS201 (including, but not limited to, C_{max}, AUC, $t_{1/2}$, Cl, V_d, Ae, CL_R) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of OPS201 and on the individual urine concentrations.

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11.4.6 Evaluation of Radiation Dosimetry

Further details on dosimetric assessments and on dosimetric parameters is provided in the SAP.

For the central dosimetry assessment, the relevant subject data (subjects' scans and data on blood activities) will be uploaded at the central reading centre and transmitted after the last scan of each visit to the central dosimetry assessment site in Würzburg. The dosimetric assessments will be performed and reported according to the criteria set by the EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting.[62].

Calculations will be conducted on the following parameters (only in organs showing uptake) as described in the Dosimetry Calculation Procedure Manual:

- organs receiving the highest absorbed dose
- specific absorbed dose per organ (Gy/GBq)
- cumulative absorbed organ doses (Gy).

Cumulative absorbed organ doses (Gy)/Organs of highest radioactivity uptake will be identified visually. Regions of interest will be placed over these organs to determine the relative radioactivity in the respective organs. TACs (describing % injected (radio)activity /region of interest (IA/ROI) of the radioactivity amount injected versus time, considering renal excretion radioactivity) will be derived. The absorbed doses of the dose limiting organs (kidney and bone marrow) will be evaluated and reported to the investigator before the next cycle can be initiated to enable radioactivity adaptations in the event the next dose may exceed the organ limits of 23 Gy (kidney) and 1.5 Gy (bone marrow). The dosimetry result for all other organs will be finalised for the final study report with the restriction, that the Part A dosimetry data must be available for the SRC meeting. These data can be reviewed at any time if a major safety issue occurs.

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11.4.7 Documentation of Biodistribution Results

Biodistribution data for target lesion and all abdominal and thoracic organs analysed will be listed for each study subject and each sampling time point. In addition, arithmetic mean, arithmetic standard deviation, coefficients of variation (CV) and number of data points (N) will be provided per sampling point. The parameters described in the Section 11.4.4 will be estimated for each subject. Total radioactivity cumulatively excreted in the urine in the interval 0 to 6 hours, 6 to 24 hours and 24 to 48 hours postinjection will be determined for each subject.

Measured total ^{177}Lu radioactivity concentrations in whole blood and urine will be listed for each study subject and each sampling time point. In addition, means, standard deviation, CV and number of data points (N) will be provided per sampling point. Based on the individual ^{177}Lu blood TACs, the concentration-time profiles of ^{177}Lu-OPS201 and the AUC in blood, will be estimated for each subject.

The proportion of renally excreted radioactivity, whole blood radioactivity, and dosimetric whole body images will be used to calculate the dosimetry of ^{177}Lu-OPS201.

11.4.8 Evaluation of Tumour Response

Tumour response will be evaluated by the site investigator and by an independent central review. Response and progression will be evaluated using the revised RECIST guideline (v1.1, see Appendix 2) 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 DCR will be calculated for both the central and the investigator review.

Time to PFS according to RECIST v1.1 and time to overall response will also be summarised.

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

Tumour volume changes as percentage change from baseline will be evaluated for:

- Part A: sstr2 lesions are identified as having visible uptake of ^{177}Lu-IPN01072 on SPECT/CT. Only the lesions monitored in dosimetry are included.
- Part B: sstr2 lesions are identified by the prestudy sstr2 scan. The lesions that are identified on PET or SPECT by sstr2 scan as measured by CT/MRI scan will be the target lesions CCI [redacted]

This will be provided on a tumour basis and the sum of the percentage change per tumour.

An onco-radiologist's global assessment of each subject will be provided to detail the observed changes and anything of note that is not captured in the other radiological evaluations, e.g. a PR or SD was not scored because of two-pixel differences.

All radiological assessments will be detailed in an Imaging Review Charter.

11.4.9 Adjustment for Country/Centre Effect

Not applicable, as no randomisation or stratification will be performed in this study.

11.4.10 Safety Evaluation

The safety endpoints are indicated in Section 3.2.1 and Section 0.

All safety analyses and summary tables will be based upon the safety population.

All AEs will be coded according to the MedDRA (v20.0 or later) and will be classified by MedDRA PT and system organ class (SOC). Adverse event listings will be presented by subject, SOC and PT.

The incidence of all reported AEs/treatment emergent AEs (TEAE), AESIs and SAEs will be tabulated by study part and overall. In addition, summary tables will be presented by maximum severity, drug relationship, and AEs/TEAEs associated with premature withdrawal of study medication or with delayed administration/reduction of ^{177}Lu-OPS201.

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

- It was not present prior to receiving the first dose of IRPP or OPS301 if applicable or;
- It was present prior to receiving the first dose of IRPP or OPS301 if applicable but the intensity increased during the active phase of the study, or;
- It was present prior to receiving the first dose of IRPP or OPS301 if applicable, the intensity is the same but the drug relationship became related during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

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

The number of subjects presenting with at least one DLT will be tabulated and listed. The type of DLTs will be also tabulated and listed.

Concomitant medication will be coded by using WHO Drug Dictionary and will be summarised by study part and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, standard deviation and range as appropriate) by study part and by overall will be presented for vital signs, blood pressure, heart rate, clinical laboratory tests etc. at each assessment with change from Baseline.

Physical examination: frequencies and severity (not clinically significant, clinically significant) of abnormalities will be analysed.

Descriptive summaries of 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 laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented.

Haematological and biochemical toxicities will be recorded and graded according to the NCI CTCAE. The NCI CTCAE Grade 3 and 4 haematology and biochemistry parameters by subject and by cycle will be tabulated and listed. For white blood cells, neutrophils, platelets and haemoglobin, with associated Grade 3 or 4 toxicities, nadir and day to nadir will be calculated.

Also, descriptive summaries will be performed for the efficacy data, the data from the quality of life questionnaire, the dosimetry data, the bone marrow safety data and the renal toxicity data for each time point as applicable.

11.5 Subgroup Analyses

Not applicable.

11.6 Interim Analyses/Safety Review Committees/Data Review Boards

Dosimetry evaluation will be performed on an ongoing basis. After the first six subjects included have completed the study Part A (EOCT/EW 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 (see Figure 13 and Appendix 3).

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.

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.

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.

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.

12 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 13.4, and to any other locations used for the purpose of the study in question (e.g. laboratories).

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

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations

13.1.1 Protocol Amendments

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

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- ***Nonsubstantial amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs or regulatory authorities for information purposes.

- ***Substantial amendments*** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects;
  - the scientific value of the study;
  - the conduct or management of the study; or
  - the quality or safety of the study drug used in the study.

  Substantial amendments must be submitted to and approved by the IECs and relevant regulatory authorities, according to local regulations, prior to implementing changes.

Urgent amendments are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the sponsor with subsequent IECs and regulatory authority notification, forthwith

The principal investigator and the sponsor will sign the protocol amendment.

13.1.2 Protocol Deviations and Exceptions

All protocol deviations will be identified and recorded by the sponsor or sponsor's representative.

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

Generally, a protocol deviation qualifies as major if:

- The deviation has harmed or posed a significant or substantive risk of harm to the research subject
- The deviation compromises the scientific integrity of the data collected for the study
- The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s)
- The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures
- The deviation is inconsistent with Ipsen's research, medical, and ethical principles. See also Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

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

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will

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

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

13.3 Study Monitoring

This study will be monitored at all stages by the clinical research personnel designated by the sponsor. Monitoring will include visits and telephone communication to ensure that the investigation is conducted according to the Protocol and complies with GCP guidelines and applicable regulatory requirements. On-site review of eCRFs will include a review of forms for completeness, clarity and consistency with source documents available for each subject.

Source data as defined by ICH GCP are all original documents, records and data as for example hospital records, laboratory notes, subject diaries or imaging data.

To this end, the investigator agrees to allow regular visits (frequency depending on recruitment) by the study monitors and to ensure they have a suitable area in which to work (e.g. a desk) and adequate access to study personnel and documents.

On-site monitoring will include source document verification (SDV). SDV is the procedure whereby the data contained in the eCRFs are compared with the primary source data (e.g. subject notes, original recordings from automated instruments, X-ray films, ECG tracings, and laboratory results) contained in the subject records held at the investigational site and thereby verified as accurate.

The investigator must be aware that:

- SDV is a part of the normal monitoring process. It will be carried out by designated study personnel and will be done in such a way as to preserve subject confidentiality, taking into account all ethical and legislative requirements. SDV will be carried out by direct comparison of entries made in the eCRF with appropriate source data. Direct access to source data requires that the subject gives written, documented consent to this.
- Where source data are in the form of a computer print-out (e.g., medical records, ECG tracings) they will be made available by the investigator to the monitor. Each will be signed and dated by the investigator or a designated person, confirming that the print-out is a true and faithful record of the data for that subject. These print-outs will be filed on-site.
- 100% Source data verification is required for this study. A source data location form will be agreed with the investigator listing all documents considered to be source data along with location and documented in the Initiation Visit Report.

For all subjects, subject identity (year of birth, sex, initials and subject number), record of entry into the study and signature of informed consent must be verified from source documents as a minimum.

It is important that the subject's notes record important details about their participation in the study. The investigator or designated person will agree, as a minimum requirement, to record the following information in the subject's notes:

- study number, brief description or title of study
- date that the subject gave written consent
- all visit dates
- all SAEs
- all concomitant medications.

The extent of source data verification and monitor visits frequency will be adapted for individual sites in case of lack of quality or a high number of protocol deviations. All trial-specific monitoring procedures, monitoring visits, frequency and extent of source data verification will be predefined in a trial specific monitoring plan.

Medical experts and CRAs may request to witness subject evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organised by the sponsor to ensure acceptable protocol execution.

The study may be audited or inspected by the sponsor (or a designated CRO), Regulatory or Health Authority or IEC/IRB. If such an audit or inspection occurs, the investigator must agree to allow access to the study site, required subject records and study documents. If notified of audits/inspections by bodies other than the sponsor, the investigator is to notify the sponsor of any such inspection immediately. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and Regulatory Authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the eCRF generation, where clinically appropriate. The investigator will be informed about the outcome of the audit.

Quality control procedures regarding statistical analysis will be documented in the SAP. Quality control procedures regarding calibration measures have to be performed according to the guidelines of the EANM [63] and will be available for review by the monitor.

13.4 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a quality assurance personnel designated by the sponsor, or by regulatory bodies. The investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable EC with direct access to any original source documents.

The investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the sponsor. The sponsor should be notified of any projected delays, which may impact the completion of the study.

13.5 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 12).

13.6 Data Quality Assurance

Monitored eCRFs will be reviewed by the CRO Data Management group for completeness, consistency, legibility and protocol compliance.

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

14 ETHICS

14.1 Compliance with Good Clinical Practice and Ethical Considerations

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

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

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

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

14.2 Informed Consent for Participation in the Study

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

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

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

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

14.2.1 Optional Informed Consent for [redacted]

[redacted] and storage for up to 15 years (where local regulations allow). A specific informed consent is required for the collection of these samples and will be explained after the subject has given written informed consent for the main study.

Subjects must receive an explanation that they are completely free to refuse to enter the exploratory part of the study and may withdraw from it at any time and for any reason up to 15 years after the end of the study and will still be allowed to take part in the main study

14.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

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

The following documents should be submitted to the relevant EC(s) for review and approval to conduct the study (this list may not be exhaustive):

- protocol/amendment(s) approved by the sponsor,
- currently applicable IB or package labelling,
- relevant investigator's curriculum vitae,
- subject information and informed consent document(s) and form(s),
- subject emergency study contact cards,
- recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) IB; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the EC will be notified about the study completion.

14.4 Confidentiality Regarding Study Subjects

The investigator must record subject identification data for all subjects who provide informed consent, regardless of whether they receive any study medication. A subject identification list, allocating subject's clear names to the study identification, must be kept in the Investigator Site File (ISF) and must allow for the definite identification of any subject that takes part in the study. Study monitors are allowed to review the list, but must not take and keep copies.

The subject's consent, study participation, the trial visits, relevant medical data, concomitant treatment and the occurrence of AEs must be documented in the subject's medical records.

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. To protect the subject's identity, a unique subject identification code will be assigned to each study subject. This unique identification number will be assigned automatically by the electronic data capture (EDC) system when the subject is first entered and will be used in lieu of the subject's name when the investigator reports AEs and/or other trial related data (e.g., eCRFs and other documents or image material submitted to the sponsor). Thus, this number will appear on all study-related records for a particular subject. Personal information will be treated as confidential, but may be reviewed for the purpose of verifying data recorded on the eCRF by the sponsor, coordinating investigator, the clinical and medical monitors, the quality assurance unit, the IEC/IRB and Regulatory Authorities. The data protection principles of GCP, Directive 95/46/EC and local data protection regulations will be observed.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Recording of Study Data

Data obtained will be collected in an eCRF. The eCRF will be completed and monitored in accordance with the principles of GCP.

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents are original documents, data and records, such as laboratory printouts, ECG reports, dispensing records, and subject files. Imaging data for all subjects will be recorded electronically on digital media. These data and print-outs will be considered as source.

The eCRF includes recordings of all study data from each subject. An eCRF record must be completed for every subject who signs an informed consent form and enters the study.

If any information is not available, and it is considered by the investigator that it will never be available (e.g. the weight on a particular visit was not recorded), the investigator will document the missing value in the eCRF and, if appropriate, explain, in a comment in the eCRF, why the investigation was missed out (e.g. the subject was not well enough to undergo the procedure). Details on the statistical analysis of missing data will be described in the SAP.

15.2 Data Management

The designated CRO will be responsible for data processing and quality control. Data management will be carried out as described in the CRO's SOPs. This includes generation and resolution of manual electronic data queries. All planned data management procedures will be documented in a study specific Data Management Plan prior to start of the trial. All planned validation checks will be documented and described in a study specific Data Validation Plan.

The electronic database is located at the EDC system vendor. Data entry and correction will be tracked by a validated electronic audit trail. All systems are validated and compliant to the FDA's ordinance 21 CFR part 11.

Adverse events, baseline findings, medical/surgical history will be coded using MedDRA terminology (v20.0 or later). Medications will be coded using the WHO Drug Dictionary (WHO-DD). The processes used for coding will be specified in the Data Management Plan.

15.3 Record Archiving and Retention

Following the end of the study it will be the responsibility of the investigator to guarantee adequate storage at the site for all study records, including the hospital notes, according to ICH

GCP and regulatory requirements and local regulations. If he/she leaves the employment at the hospital he/she will inform the sponsor and nominate a contact person who will have access to the study documents. The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents shall be archived in such a way that ensures that they are readily available upon authorities' request.

The ISF must not be destroyed without the sponsor's approval. The investigator's contract will contain all regulations relevant for the study centre.

16 FINANCING AND INSURANCE

16.1 Contractual and Financial Details

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

Each investigator who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to applicable legal and FDA 21 CRF Part 54 requirements. All relevant documentation will be filed in the trial master file (TMF) and/or ISF, as appropriate.

16.2 Insurance, Indemnity and Compensation

Where required by the laws and regulations of the country in which the study is performed, insurance of subjects against health impairment occurring as a result of participation in the study will be set up in accordance with said laws and regulations. All relevant documentation regarding such insurance will be filed in the TMF and/or ISF, as appropriate.

Indemnification

With respect to any injury caused by the study drug to the subject during this study, the sponsor assumes liability by law on behalf of the investigator(s); provided, however, (a) that the investigator(s)/delegate have conducted this study in accordance with this protocol and any amendments thereto, all instructions delivered by the sponsor, all laws and regulations, accepted standards of medical and clinical practice and GCP Guidelines, and scientific practice and currently acceptable techniques and know-how; and (b) that the study drug administered to the subject in this study has been supplied by the sponsor, and administered/used in accordance with this protocol. The indemnity will not cover injuries to the extent caused by the investigator(s)'/delegate's negligence or wilful misconduct, or failure to follow this protocol or written instructions (unless deviation to protect safety of the subject) or failure to obtain proper informed consent from the subject. The sponsor shall have the sole right to select defence counsel, direct the defence, settlement, or other disposition of any claims, and the investigator(s)/delegate shall cooperate in the defence of any claim.

The subjects are covered by insurances held by the sponsor.

17 REPORTING AND PUBLICATIONS OF RESULTS

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Clinical study

reports (CSRs) covering clinical and biometric aspects of the study will be generated at the end of the study.

17.1 Publication Policy

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

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee.

Selection of authors for scientific publications will follow the International Committee of Medical Journal Editors guidelines.[64] In particular, those named as authors, whether employed by an Ipsen affiliate or sponsor, or external investigators, 'should have participated sufficiently in the work to take public responsibility for the content'.
Authorship credit should be based on:

- Substantial contributions to the conception and design, or acquisition of data, or analysis and interpretation of data;
- Drafting the article or revising it critically for important intellectual content;
- Final approval of the version to be published;
- Agreement to be accountable for all aspects for the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

All authors of a manuscript should meet all four criteria. Each author must agree to their inclusion in the list of authors.
Resolution of scientific differences in the presentation or interpretation of study findings will be conducted along principles of honest scientific debate. The sponsor shall be promptly notified of any amendments subsequently requested by referees or journal editors.

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

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

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

Publication of subgroup data and single centre data shall not be performed until the complete study has been published.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator / institution.

17.2 Clinical Study Report

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

A final CSR will be prepared after the last subject completes the 2-year long-term follow-up period.

Analysis of biobank samples will be performed outside the scope of the main study and reported separately.

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