PROTOCOL TITLE: A MULTICENTRE, OPEN-LABEL PHASE I/II STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIODISTRIBUTION AND ANTI-TUMOUR ACTIVITY OF ^{177}LU-OPS201 WITH COMPANION IMAGING ^{68}Ga-OPS202 PET/CT IN PREVIOUSLY TREATED SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC CANCERS EXPRESSING SOMATOSTATIN RECEPTOR 2 (SSTR2)

(Sub-study of Master Protocol Ipsen 001 Version 1.0 dated 02 February 2018)

STUDY PROTOCOL

STUDY number: D-FR-01072-002

^{68}Ga-OPS202 and ^{177}Lu-OPS201

EudraCT number: 2017-005173-39/NCT Number: XXXX

Version 2.0: 07 March 2019

Study Sponsor:

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INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01072-002 entitled a multicentre, open-label phase I/II study to evaluate the safety, tolerability, biodistribution and anti-tumour activity of ^{177}Lu-OPS201 with companion imaging ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic cancers expressing somatostatin receptor 2 (sstr2). 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:
OFFICE: [ ]
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Sponsor's Representative Signature:

NAME: PPD
TITLE: PPD Ipsen Bioscience Inc
SIGNATURE:

DATE:
OFFICE: [ ]
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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01072-002 entitled a multicentre, open-label phase I/II study to evaluate the safety, tolerability, biodistribution and anti-tumour activity of ^{177}Lu-OPS201 with companion imaging ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic cancers expressing somatostatin receptor 2 (sstr2). 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.

NAME: PPD

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01072-002 entitled a multicentre, open-label phase I/II study to evaluate the safety, tolerability, biodistribution and anti-tumour activity of ^{177}Lu-OPS201 with companion imaging ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic cancers expressing somatostatin receptor 2 (sstr2). 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.

NAME: PPD

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

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SUMMARY OF CHANGES

The current version of the protocol was released on 07 March 2019 and includes Amendment 1. For all protocol amendment/s, amendment form/s were prepared and are provided in the Appendices listed in Table 1. All modifications (except minor changes) are presented in the appendices.

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	07 March 2019	Appendix 2

SYNOPSIS

Name of sponsor/company: IPSEN

Name of finished product:

^{177}Lu-OPS201 – ^{177}Lu-satoreotide tetraxetan

^{68}Ga-OPS202 – ^{68}Ga-satoreotide trizoxetan

Name of active ingredient(s):

^{177}Lu-OPS201 – INN for OPS201 is satoreotide tetraxetan

^{68}Ga-OPS202 – INN for OPS201 is satoreotide trizoxetan

Title of study: a multicentre, open-label phase I/II study to evaluate the safety, tolerability, biodistribution and anti-tumour activity of ^{177}Lu-OPS201 with companion imaging ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic cancers expressing somatostatin receptor 2 (sstr2).

(Sub-study of Master Protocol Ipsen 001 Version 1.0 dated 02 February 2018)

Study number: D-FR-01072-002

Number of planned centres:
Phase I: Approximately 8 centres in Europe and United States of America
Phase II: Approximately 30 centres in Europe, North America and Asia-Pacific

Planned study period:	**Phase of development**:
Phase I: FPI: Q4 2018 - LPO: Q2 2020 (core treatment part) Phase II: FPI: Q4 2020 - LPO: Q1 2022 (core treatment part) - Q4 2023 (2-year follow-up part)	Phase I/II

Objectives:

Primary objective

Phase I

To evaluate the safety and tolerability and to define the maximum tolerated cumulative activity (MTCA) of fractionated intravenous (i.v.) administration over two cycles of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 Positron Emission Tomography/Computed Tomography (PET/CT) scans.

Phase II

To evaluate the objective response rate (ORR) of fractionated i.v. administration of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans.

Secondary objectives

Phase I

- To determine the whole-body distribution and pharmacokinetics (PK) of ^{177}Lu-OPS201 after each administration.
- To determine the radiation dosimetry of ^{177}Lu-OPS201 (organ exposure to radiation) after each administration.

- To determine the PK of OPS201 in plasma and urine.
- To describe the preliminary anti-tumour activity of ^{177}Lu-OPS201.
- To evaluate progression free survival (PFS) until Long-term Follow-up Visits up to 2 years after the end of core trial (EOCT) Visit.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 Single Photon Emission Computerised Tomography (SPECT)/CT.
- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT and tumour response to ^{177}Lu-OPS201.

Phase II

- To evaluate the efficacy of ^{177}Lu-OPS201 using Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 and/or Positron Emission Tomography Response Criteria In Solid Tumours (PERCIST) v1.0 criteria, volumetric CT and modified PERCIST using ^{68}Ga-OPS202 PET scans and modified RECIST using the ^{68}Ga-OPS202 avid lesions.
- To evaluate PFS until Long-term Follow-up Visits up to 2 years after the EOCT Visit.
- To estimate the 1-year overall survival (OS) rate.
- To further evaluate the safety profile of 177Lu-OPS201.
- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT with tumour response to ^{177}Lu-OPS201 therapy.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 SPECT/CT.
- To evaluate the impact of ^{177}Lu-OPS201 on the health-related quality of life of treated subjects.
- To estimate the proportion of sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by standardised uptake volume (SUV) in subjects screened for ^{177}Lu-OPS201 treatment.
- To further assess some PK and dosimetry parameters of ^{177}Lu-OPS201 based on the phase I results.

Exploratory objectives

Phase I/II

- To explore renal and haematological safety by measuring urinary specific biomarkers and deoxyribonucleic acid-double strand breaks (DNA-DSB) and DNA repair capacity in peripheral lymphocytes (at selected centres).
- To evaluate the tumour microenvironment, transcriptomics, DNA repair, gene mutation in tumour as compared to germinal mutation and other markers of interest through assessment of tumour biopsies.
- To collect biobank samples for future analysis of circulating markers (optional, additional informed consent required).
- To evaluate the association between the tumour uptake of ^{68}Ga-OPS202 and sstr2 expression on tumours as determined by immunohistochemistry (IHC).

- To generate a model integrating PK, pharmacodynamics, dosimetry, anti-tumour activity and safety data if warranted by the data.

Study hypothesis:

Phase I

^{177}Lu-OPS201 will be sufficiently safe to permit clinical investigation in phase II when administered in previously treated subjects with limited disease (LD)- or extensive disease (ED)- small cell lung cancer (SCLC) and in previously treated metastatic hormone receptor positive (HR+) / human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC), expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans (see eligibility criteria).

Phase II

Previously treated subjects with LD- or ED-SCLC, or metastatic HR+/HER2- BC expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans and treated with ^{177}Lu-OPS201 will attain a clinically meaningful ORR, which is superior to the historical ORR obtained by current standard-of-care (SoC) treatment.

Methodology:

Study design:

This is a phase I/II, multicentre, open-label single-arm study of ^{177}Lu-OPS201 therapy with companion diagnostic imaging ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic solid tumour expressing sstr2 who progressed under or after, failed to respond to, or are intolerant or having a contraindication to available SoC treatment options and are deemed suitable for treatment with ^{177}Lu-OPS201 as per the investigator's clinical assessment and/or their individual disease state. More specifically:

- Subjects who had ED-SCLC at presentation who have progressed on or after one line of standard chemotherapy. If a subject had LD-SCLC at presentation and received surgery and/or radiotherapy as first line treatment (with or without chemotherapy) and has localised relapse, further local treatment (such as surgery) should be considered in addition to the chemotherapy options.
  For subjects with either ED-SCLC or LD-SCLC, if subjects relapse more than 6 months after first-line treatment, re-treatment with their initial regimen is recommended. Subjects may have received prior immunotherapy.
- Subjects with HR+/HER2- metastatic BC after failure of prior SoC treatments and who have received, if indicated, at least one line of hormonal therapy, cyclin-dependent kinase (CDK) 4/6 inhibitor for advanced or metastatic disease and at least one line of chemotherapy for metastatic disease; subjects with *BRCA*-mutated metastatic disease who may have received a poly adenosine diphosphate ribose polymerase (PARP) inhibitor, if available, are eligible; prior adjuvant hormonal treatment and prior adjuvant chemotherapy are allowed.

Before any study-specific procedures with ^{177}Lu-OPS201, subjects will be administered ^{68}Ga-OPS202 and PET/CT images will be acquired. Focal avid lesion will be interpreted as sstr2-positive if the uptake is 1.5-fold or greater than the non-tumour liver and lung tissue is noted and if subjects have at least two avid lesions of ≥20 mm in the longest diameter on ^{68}Ga-OPS202 PET/CT scan. Furthermore, subjects will be considered eligible for treatment with ^{177}Lu-OPS201 if the imaging core laboratory (ICL) confirms ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on

^{18}F-fluorodeoxyglucose (FDG)-PET/CT and if the subjects meet all the other protocol eligibility criteria.

The study consists of two phases: phase I with ^{177}Lu-OPS201 radioactivity escalation and peptide mass dose escalation, and phase II assessing the efficacy of ^{177}Lu-OPS201 in subjects in selected indications, in a basket design. A clinical research Master Protocol will encompass this biomolecular target study protocol together with other study protocols targeting the same receptor (sstr2) and will describe the overall background, rationale, objectives, design, methodology and organisation of the overall sstr2-positive cancer research project for OPS201 and OPS202.

Phase I:

During phase I, it is planned to enrol subjects with tumours expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans in a basket design initially including SCLC and HR+/HER2- BC. Further types of tumours may be added according to advances in the preclinical and clinical knowledge on ^{68}Ga-OPS202 and ^{177}Lu-OPS201 and emerging clinical and non-clinical published data.

Core treatment (two first cycles)

In the core treatment period of phase I, up to three radioactivity levels of ^{177}Lu-OPS201 are planned to be tested with the radioactivity delivered in two administrations: one loading dose followed by a lower maintenance dose, 6 weeks apart (+ up to additional 4 weeks in case of adverse events (AEs) that need to be adequately recovered). It is anticipated that three cohorts of three to five subjects in each cohort will be included in the radioactivity escalation of phase I.

A treatment cycle is defined as the timeframe of 6 (up to 10) weeks between two administrations or the timeframe of 6 weeks following the last administration. In case of logistical issues, the cycle could be extended by up to additional 2 weeks.

The size of the cohorts will be three to five subjects. Once five subjects are enrolled in a cohort, enrolment will be stopped in that cohort. A cohort will be considered as evaluable once three subjects of the cohort complete Cycle 2 or discontinue early during Cycle 2. Cohorts will be enrolled using the following escalation approach (Table S1):

- starting cumulative radioactivity of 9 GBq of ^{177}Lu-OPS201 fractionated into one administration of 6 GBq followed by a second administration of 3 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).
- maximum cumulative radioactivity of 12.9 GBq of ^{177}Lu-OPS201 fractionated into two administrations, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).
- maximum radioactivity administrable in one cycle is 7.4 GBq of ^{177}Lu-OPS201.
- the inter-cohort radioactivity escalation will be performed by maximum increment of 2 GBq.

Table S1 Radioactivity Escalation Plan (Irrespective of Peptide Mass Dose)

Planned radioactivity escalation	Cohort 1 and 2	Cohort 3 and 4	Cohort 5 and 6
Cumulative (GBq)	9	11	12.9
Schedule (GBq)	6 + 3	7 + 4	7.4 + 5.5

Abbreviation: GBq=Gigabecquerel.

Each subject will only participate in one cohort.

Proceeding to the second administration

Data review will take place before the second cycle of each subject in a cohort based on all available safety and dosimetry data from the subject. The decision to proceed to second administration will be done as follows:

- subjects with dose limiting toxicities (DLTs) after first administration will be discontinued from ^{177}Lu-OPS201 treatment.
- subject will be eligible for second administration of ^{177}Lu-OPS201 only if:
  - blood cell counts and renal function tests are in the range defined in the study inclusion criteria (#7), within the treatment cycle
  - subject's organ absorbed doses did not exceed 1.5 Gy in bone marrow (BM) and 23 Gy in kidney.

  The radioactivity dose of the second administration will be adjusted based on dosimetry results to prevent exceeding limiting organ absorbed doses limits (1.5 Gy for bone marrow; 23 Gy for kidney).

Proceeding to radioactivity escalation

Data review board (DRB) for radioactivity escalation will take place after the third subject of each cohort has received two cycles of ^{177}Lu-OPS201 with DLT assessments performed. The DRB will review all available safety and dosimetry data from the study to decide the radioactivity level that will be administered in the next cohort.

If no DLT is observed, the radioactivity will be escalated by 2 GBq in the next cohort of radioactivity escalation using the following guidance (Table S1):

- if 6 GBq followed by a second administration of 3 GBq is well tolerated, escalate to 7 GBq followed by a second administration of 4 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).
- if 7 GBq followed by a second administration of 4 GBq is well tolerated, escalate to 7.4 GBq followed by a second administration of 5.5 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).

However, if DLTs are reported, a statistical Bayesian modelling approach will be implemented to produce a more precise dose-DLT and dose-organ radiations dose curve to guide the dose selection and predict a radioactivity level not exceeding the MTCA/maximum tolerated single activity (MTSA) that could be tested in the next cohort of radioactivity escalation.

Proceeding to radioactivity de-escalation

If the starting cumulative radioactivity of 9 GBq is not well tolerated, another cohort with a decreased cumulative radioactivity will start. In this case, the cumulative radioactivity could be 7.5 GBq (one administration of 4.5 GBq followed by an administration of 3 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered)).

The MTCA is defined as the maximum cumulative radioactivity that may be administered following fractionated i.v. administrations of at least 6 weeks apart, so that:

- no more than 33% of the subjects experience a DLT after first or second administration of ^{177}Lu-OPS201 and/or

- no more than 10% of the subjects have cumulative absorbed dose in each target organ exceeding the acceptability limits (1.5 Gy in BM and 23 Gy in kidney) after second administration of ^{177}Lu-OPS201.

The MTSA is defined as the highest single radioactivity that can be given so that no more than 33% of the subjects experience a DLT during Cycle 1. The MTSA will be determined in case of unacceptable toxicity seen after first administration of ^{177}Lu-OPS201.

The radioactivity escalation will be stopped as soon as:

- the MTCA and/or MTSA have been defined with good precision; or
- the maximum planned radioactivity of 12.9 GBq, fractionated into two administrations separated by 6 weeks (+ up to additional 4 weeks in case of AEs that need to be adequately recovered), is administered without safety concerns and is thus defined as the maximum administrable cumulative activity (MACA).

Once the radioactivity escalation has been completed, the MTCA level may be repeated in a last cohort of three to five subjects with the same peptide mass dose (300 µg ±15%) to confirm the safety profile. If the MTCA is not reached and if limiting organ dose levels are not exceeded at the highest planned radioactivity (12.9 GBq) and if no individual withdrawal criteria are met, an additional cohort with a higher cumulative radioactivity may be planned.

Note: an application for a substantial amendment will be submitted for approval by the Competent Authorities (CAs) and/or Ethic Committees (ECs) (as applicable) before initiating changes to the study conduct.

The DLTs are defined for any of the following investigational radiopharmaceutical product (IRPP)-related AEs according to National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) scale version 5.0 that occur during the defined DLT assessment period (from the first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration):

- Grade 4 neutropenia lasting for seven or more consecutive days.
- Grade 3 and 4 febrile neutropenia.
- Grade 4 thrombocytopenia for seven or more consecutive days.
- Grade 3 thrombocytopenia complicated by a bleeding event.
- Grade 4 anaemia.
- Grade 3 anaemia requiring transfusion.
- Grade 3 or higher laboratory abnormalities of aspartate amino transferase/alanine amino transferase (AST/ALT) and/or bilirubin, with the following exceptions:
  - for subjects with Grade 1 AST/ALT at baseline (>upper limit of normal (ULN) to 3xULN), a AST/ALT value of >7.5xULN will be considered a DLT.
  - for subjects with Grade 2 AST/ALT at baseline (>3xULN to 5xULN), a AST/ALT value >10xULN will be considered a DLT.
- any Grade 3 or higher acute kidney injury (creatinine >3x baseline or >4.0 mg/dL).
- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate supportive care
  - Grade 3 fatigue lasting less than a week

- Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, is not clinically complicated and resolves spontaneously or with conventional medical interventions
- Grade 3 or higher amylase or lipase not associated with symptoms or clinical manifestations of pancreatitis

• any toxicity related to ^{177}Lu-OPS201 resulting in a treatment delay of more than 4 weeks due to delayed recovery to baseline or resolution of any AE of Grade 2 or more (exception of alopecia and lymphopenia).

• Grade 5 toxicity (death)

The EOCT visit will be done 6 weeks after last ^{177}Lu-OPS201 dose administration, and subjects will be followed-up until resolution of any AE of Grade >1. Subjects who discontinue study treatment for reasons other than disease progression (e.g. toxicity) should continue to undergo scheduled tumour assessments until the subject dies, withdraws consent, or until the study closes, whichever occurs first.

Optional additional cycles

If a subject tolerates well the treatment and shows clinical benefit (e.g. complete response (CR), partial response (PR), or stable disease), up to four additional cycles of ^{177}Lu-OPS201 administration every 6 weeks (+ up to additional 4 weeks in case of AEs that need to be adequately recovered) can be administered to this subject. Dosimetry will be performed after each additional cycle and the radioactivity dose administrated will be adjusted based on dosimetry results to prevent exceeding limiting organ absorbed doses limits (ie, 23 Gy in kidney, 2 Gy in bone marrow if no Grade 3 or more haematotoxicity have been observed in this subject, otherwise limit in bone marrow is set to 1.5 Gy). For these subjects, an end of additional cycles (EOAC) visit will be done 6 weeks after last ^{177}Lu-OPS201 dose administration.

Of note, the decision to administer additional cycles or any other anti-tumoural treatment is left at the investigator's and subject's discretion and must be discussed with and confirmed by the sponsor.

Peptide mass dose evaluation

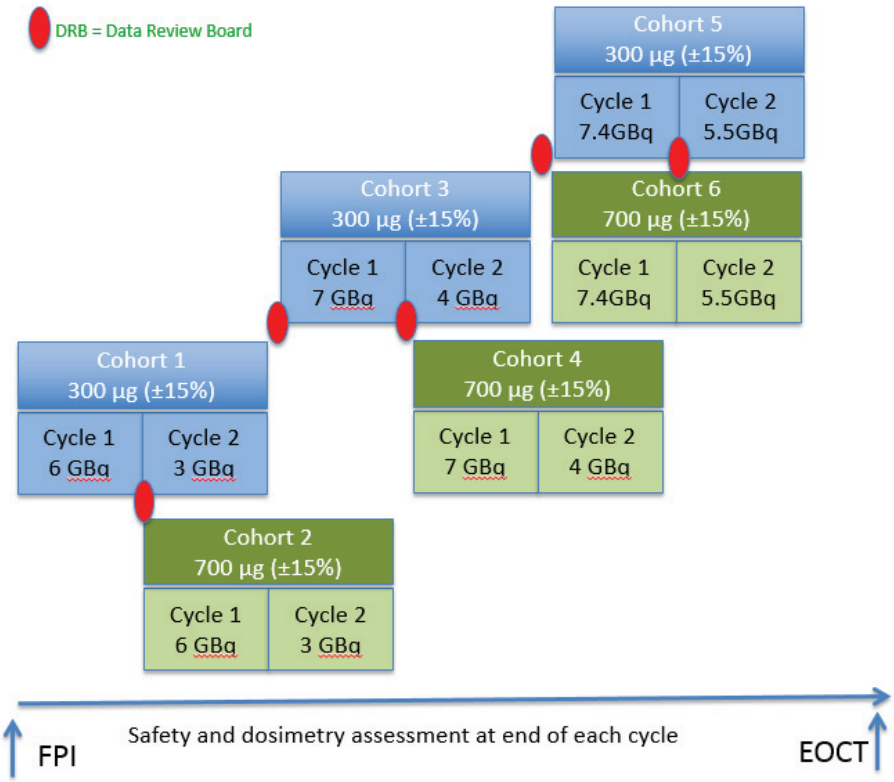
In parallel with the radioactivity escalation phase, once the first cycle of a radioactivity level is considered acceptably tolerated by the DRB, the same radioactivity level will be repeated with a higher peptide mass dose (700 µg (±15%)). Three additional cohorts of three to five subjects will thus be enrolled in the peptide mass dose evaluation (see Figure S1). The schedule of assessments and safety evaluation in these cohorts will be the same as in the radioactivity escalation cohorts.

The DRB for peptide mass dose escalation will meet after the third subject of each previous radioactivity escalation cohort has received the first cycle of ^{177}Lu-OPS201 with DLT assessments performed. The DRB will review all safety and dosimetry data and allow the peptide mass dose escalation. The cohort with the high peptide mass dose (700 µg) will thus only start when the first cycle of the corresponding radioactivity level tested with 300 µg peptide mass dose has been evaluated by the DRB and has been considered acceptably tolerated, except for the cohort 6 where the radioactivity for the first cycle (7.4 GBq) is slightly different from the previous cohort (7.0 GBq) (see Figure S1) The same subject cannot participate in the radioactivity escalation cohort and the peptide mass dose cohort.

Long-term follow-up

A long-term follow-up period will start after EOCT or after EOAC visit until 24 months maximum in total. Subjects will be followed-up every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first.

Figure S1 Initial Phase I Study Design



Abbreviations: EOCT=end of core trial, FPI=first patient in, GBq=Gigabecquerel.

Phase II

Upon termination of phase I radioactivity escalation, peptide mass dose evaluation and/or determination upon reaching MTCA and stated jointly by the DRB and the sponsor, and in consideration of the accumulated subject data, a phase II will be started enrolling cohorts of subjects with sstr2-positive tumours as identified by ^{68}Ga-OPS202 PET/CT scans to evaluate the efficacy and to confirm the safety of ^{177}Lu-OPS201. Phase II will be conducted with indication-specific cohorts using a Simon's optimal two-stage design.

Two cohorts will be initially investigated with ^{68}Ga-OPS202 and ^{177}Lu-OPS201: previously treated subjects with LD- or ED-SCLC or metastatic HR+/HER2- BC. Pending the results generated during the ongoing studies, advances of scientific and clinical knowledge and emerging published data, other cohorts could be initiated in this study.

Note: an application for a substantial amendment will be submitted for approval by the CAs and/or ECs (as applicable) before initiating changes to the study conduct.

Before any study-specific procedures with ^{177}Lu-OPS201, subjects will be administered ^{68}Ga-OPS202 and PET/CT images will be acquired. Focal avid lesion will be interpreted as sstr2-positive if the uptake is 1.5-fold or greater than the non-tumour liver and lung tissue is noted and if subjects have at least two avid lesions of ≥20 mm in the longest diameter on ^{68}Ga-OPS202 PET/CT scan. Furthermore, subjects will be considered eligible for treatment with ^{177}Lu-OPS201 if ICL confirms ≥50% matching between the lesions

detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT and if the subjects meet all the other inclusion criteria and none of the exclusion criteria.

Dosing of ^{68}Ga-OPS202 and PET image acquisition time as well as the eligibility criteria for sstr2 positivity could be revised at the start of phase II should emerging data from phase I and ongoing studies support modifications specific to these sstr2 expressing tumours.

Note: an application for a substantial amendment will be submitted for approval by the CAs and/or ECs (as applicable) before initiating changes to the study conduct.

Each cohort will enrol a defined number of subjects with sstr2-positive ^{68}Ga-OPS202 PET/CT scans (see Statistical Methods section below) and will investigate if treatment with ^{177}Lu-OPS201 attains an objective response rate (ORR or equivalent efficacy parameter) superior to a clinically accepted historical threshold of current SoC treatment for subjects with locally advanced or metastatic disease previously treated.

In each cohort, subjects will receive the recommended phase II treatment schedule supported by dose-response and exposure-response analyses of phase I data as well as data emerging from other ongoing studies in other populations, if applicable. The recommended phase II treatment schedule corresponds to a recommendation of the cumulative radioactivity, the fractionation of the radioactivity, the peptide mass dose and the dosing interval. In any case, the cumulative radioactivity administered during phase II will not exceed the MTCA/MACA determined during phase I. Additional cycles (every 6 weeks (+ up to additional 4 weeks in case of AEs that need to be adequately recovered)) can be administered to subjects at investigator's and subject's discretion, provided additional benefit could be expected and limiting organ dose levels have not been exceeded.

The current protocol may be amended at the end of the phase I to define the phase II design.

Subjects in each phase of the study will have 2-year follow-up after the end of the last ^{177}Lu-OPS201 Cycle, with a visit every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first.

An independent safety assessment committee (ISAC) structured to assess safety in addition to efficacy will be established during phase II in order to make recommendations regarding protocol modifications to reduce risks to subjects enrolled in the trial.

Number of subjects planned:

During phase I, up to 30 subjects will be enrolled for treatment with ^{177}Lu-OPS201. Based on the current knowledge on the proportion of subjects presenting with sstr2-positive tumours, it is anticipated that approximately 55 to 60 subjects will need to be administered ^{68}Ga-OPS202 for PET imaging screening.

During phase II, approximately 172 subjects (76 subjects with SCLC and 96 with BC) are planned to be enrolled for the Simon's optimal two-stage design. In this study phase, it is anticipated that approximately 340 subjects will be screened and administered ^{68}Ga-OPS202 for PET imaging. However, recruitment will be stopped once the number of required sstr2-positive subjects is reached.

Further cohorts of subjects with other types of tumours expressing sstr2 could be added in this protocol according to the advances in the preclinical and clinical knowledge on ^{68}Ga-OPS202 and ^{177}Lu-OPS201 and emerging published data on the diseases. In this case, the additional number of subjects will be estimated based on standard of care historical response (e.g. ORR/best overall response (BOR)) of the corresponding disease.

Note: an application for a substantial amendment will be submitted for approval by the CAs and/or ECs (as applicable) before initiating changes to the study conduct.

Diagnosis and criteria for inclusion for ^{68}Ga-OPS202 imaging:

Inclusion criteria:

All subjects must fulfil all the following criteria to undergo the ^{68}Ga-OPS202 imaging (phase I/II):

(1) signed informed consent prior to initiation of any study-specific activities/procedures.

(2) male (except for BC cohort) or female subject aged 18 years or older.

(3a) histologically confirmed cancer, that is locally advanced or metastatic disease, which has progressed during or after, failed to respond to, or for which there is poor tolerability or a contraindication to available SoC treatment options as per the assessment of the investigator; initially, subjects with the disease below may be considered:

(a) Subjects who had ED-SCLC at presentation who have progressed on or after one line of standard chemotherapy. If a subject had LD-SCLC at presentation and received surgery and/or radiotherapy as first line treatment (with or without chemotherapy) and has localised relapse, further local treatment (such as surgery) should be considered in addition to the chemotherapy options.

For subjects with either ED-SCLC or LD-SCLC, if subjects relapse more than 6 months after first-line treatment, re-treatment with their initial regimen is recommended. Subjects may have received prior immunotherapy.

(b) Subjects with HR+/HER2- metastatic BC after failure of prior SoC treatments and who have received, if indicated, at least one line of hormonal therapy, CDK4/6 inhibitor and/or everolimus for advanced or metastatic disease and at least one line of chemotherapy for metastatic disease; subjects with BRCA-mutated metastatic disease who may have received a PARP inhibitor, if available, are eligible; prior adjuvant hormonal treatment and prior adjuvant chemotherapy are allowed.

(4) disease must be unsuitable for curative surgical resection and must not be amenable to curative radiotherapy.

(5a) documented progressive disease (radiological, based on RECIST v1.1) within 3 months prior to first study drug administration. Screening study-related images should be sent to the ICL.
Note: All images of the two datasets documenting progression should be sent to ICL.

(6) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

(7a) adequate organ function determined within 28 days prior to ^{177}Lu-OPS201 administration, defined as follows:

- Haematological:
  - white blood cells (WBC) ≥3000/µL, with absolute neutrophil count ≥1000/µL, platelet ≥100,000/µL and haemoglobin ≥9 g/dL (without need for hematopoietic growth factor or transfusion support).
- Renal:
  - estimated glomerular filtration rate (eGFR) ≥55 mL/minute/1.73m^2
- Hepatic:
  - total serum bilirubin ≤2×ULN

- aspartate aminotransferase/ alanine aminotransferase ≤2.5×ULN (≤5×ULN if subject has liver metastases).

(8a) has a formalin fixed paraffin embedded tumour sample (archival tumour sample obtained within 1 month prior to consent) from the primary or metastatic lesion OR is willing to undergo newly obtained biopsy prior to first dose of study treatment. Subjects who are unable or do not consent to provide acceptable tissue may not be enrolled unless there has been prior agreement with the sponsor.
Note: the subject will be enrolled (if he/she fulfills all inclusion criteria and has no exclusion criterion) irrespective of the biopsy result

(9) estimated life expectancy >3 months.

Eligibility Criteria for Therapy (Phase I/II)

To receive ^{177}Lu-OPS201 therapy, each subject must fulfil all the eligibility criteria including the below criteria:

(10a) ^{68}Ga-OPS202 uptake in target tissue (primary tumour, lymph nodes and/or metastases) showing at least two avid (uptake ≥1.5 non-tumour liver and lung uptake) lesions of ≥20 mm in the longest diameter on PET/CT as confirmed by central reader.

(11) Radiologically, ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on 18F-FDG-PET/CT as confirmed by central reader

The inclusion criteria for phase II will be refined based on the results from phase I as well as type of possible additional tumours and indications to be investigated and will be documented as part of a protocol amendment.

Exclusion criteria:

Eligible subjects must not have any of the following conditions (phase I/II):

(1) male subjects with BC.

(2a) unstable central nervous system metastasis defined as (any of the following):

(a) radiographic evidence of new or progressive brain metastases after prior radiation therapy with at least one brain metastasis measuring ≥1 cm in longest diameter on gadolinium-enhanced magnetic resonance imaging (MRI), and/or

(b) imaging following prior radiation is not consistent with pseudo-progression in the judgment of treating clinician, and/or

(c) evidence of diffuse leptomeningeal disease on brain MRI or by previously documented cerebrospinal fluid cytology.
NOTE: discrete dural metastases are permitted.

Subjects with previously treated brain metastases (with no lesion measuring ≥1 cm in longest diameter on gadolinium-enhanced MRI at the time of evaluation for the study) may participate provided they are neurologically stable as defined by (all the following need to be met):

i. no evidence of progression by imaging and any neurologic symptoms have returned to baseline

ii. no use of steroids and anti-convulsants for at least 7 days prior to IRPP administration.

iii. no clinically significant mass effect, haemorrhage, midline shift, or impending herniation on baseline brain imaging.

iv. no significant focal neurologic signs and/or symptoms that would necessitate radiation therapy or surgical decompression in the judgment of the treating clinician.

(3a) centrally located lung tumours that show radiological evidence (CT or MRI) of either:
(i) cavitation or necrosis, or,
(ii) focal invasion or major blood vessels.

(4a) Subjects had received chemotherapy within the previous 4 weeks or had not recovered from adverse events due to chemotherapy. Additional exclusion criteria were previous hemibody external radiotherapy, systemic radiotherapy with radioisotopes within the previous 24 weeks.

(5) previous chemotherapy within a cycle interval, curative radiotherapy within 4 weeks or palliative radiotherapy within 7 days prior to IRPP administration.

(6) prior treatment with any other investigational medicinal product (IMP) within five half-lives of the previous IMP or within 2 weeks, if the previous compound is a mechanism-based molecularly targeted agent whose half-life is not well-characterised and toxicities have not resolved from Grade 2 or higher prior to IRPP administration.

(7) any unresolved NCI-CTCAE Grade 2 or higher toxicity (except alopecia and Grade 2 platinum-therapy related neuropathy) from previous antitumour treatment and/or medical/surgical procedures/interventions.

(8) nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study as assessed by the investigator.

(9a) history of major thrombotic or clinically relevant major bleeding event in the past 6 months putting the subject at high risk of bleeding during the study as assessed by the investigator (international normalisation ratio (INR) or prothrombin time ≥1.5xULN, unless the subject is receiving anticoagulant therapy).

(10) prior major surgery from which the subject has not sufficiently recovered.

(11a) known allergy to contrast medium product or ^{177}Lu, DOTA, OPS200, OPS301 or any of the excipients of ^{177}Lu-OPS201, as well as to ^{68}Ga-OPS202 or its excipient.

(12a) any condition that precludes the proper performance of PET and/or SPECT scans, CT scans and/or MRI:

(a) subjects who are not able to tolerate the CT contrast agent.

(b) subjects with metal implants or joint prosthesis (depending on the location, if interferes with the PET and/or CT analysis).
Notes: Subjects with metal implants cannot undergo MRI; Subjects with medical devices in situ, which do not overlap with the Volume of Interest in the opinion of the radiologist or dosimetrist or are not expected to interfere with the imaging or interpretation, can be included. The dosimetry team should be informed of the presence of a device in situ.

(c) or any other objects that might interfere with the PET and/or CT analysis.

(d) subjects unable to raise arms for prolonged imaging purposes.

(e) subjects unable to lie still for the entire imaging time.

(f) subjects weighing greater than 130 kg (287 lb).

(13a) subject with history of other malignancy within the past 3 years with the following exceptions: malignancy treated with curative intent and with no active disease and has not received chemotherapy for the last 3 years for these conditions; adequately treated non-melanoma skin cancer without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease; adequately treated breast ductal carcinoma in situ without evidence of disease; prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrolment; adequately treated superficial or in situ carcinoma of the bladder without evidence of disease.

(14) other investigational procedures while participating in this study.

(15a) clinically significant abnormalities on electrocardiogram (ECG) at screening including QTcF >450 msec for males or >470 msec for females at screening or subjects who cannot tolereate high volume load.

(16) pregnant or lactating female. Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 6 months after the last dose of ^{177}Lu-OPS201.

OR

male subject who is unwilling to use acceptable method of effective contraception during treatment and through 6 months after the last dose of ^{177}Lu-OPS201.

(17) subject likely not to be available to complete all protocol-required study visits or procedures and/or to comply with all the required study procedures to the best of the subject and investigator's knowledge.

(18a) history or evidence of psychiatric, substance abuse (except for tobacco smoking), or any other clinically significant disorder, condition or disease (including active known infection with human immunodeficiency virus (HIV) requiring systemic treatment, or known acquired immunodeficiency syndrome (AIDS)-related illness, or known active hepatitis B or C infection) that, in the opinion of the investigator or sponsor medical, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Notes: Female subjects must be either postmenopausal (any female who is age ≥55 years with cessation of menses for 12 or more months or less than 55 years and no spontaneous menses for at least 2 years or less than 55 years and no spontaneous menses within the past 1 year with postmenopausal gonadotropin and oestradiol levels) or permanently sterile, can enter the trial without taking specific contraceptive measures. Female subjects of childbearing potential must have a negative pregnancy test upon entry into this study and agree to use a highly effective method of contraception from Screening until 6 months after the last dose of ^{177}Lu-OPS201;

Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence;

True abstinence, when in line with the preferred and usual lifestyle of the subject, is considered a highly effective method only if defined as refraining from heterosexual

intercourse during the entire period of study participation and for 6 months after the last dose of ^{177}Lu-OPS201. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception; and

Male subjects must be either surgically sterile or agree to use a double-barrier contraception method from Screening until 6 months after the last dose of ^{177}Lu-OPS201.

Egg cell and sperm donation are not permitted during the contraception period (up to 2 years after the study).

Test product, dose, mode of administration:

Investigational Imaging Product (IIP), ^{68}Ga-OPS202:

The IIP is a solution for injection prepared prior to administration from a radiolabelling "cold" kit and a ^{68}Ge/^{68}Ga-generator. The radiolabelling kit consists of two vials; one containing lyophilised OPS202 and excipients and a second containing a solution for reconstitution. After QC sampling, QC testing and release, the volume to be administered to the subject is withdrawn from the IIP vial, containing up to 45 µg OPS202. This volume is determined to obtain the target radioactivity at the time of administration, considering the decay of ^{68}Ga. All subjects will receive a single dose of IIP (one at screening and another at EOCT), with ^{68}Ga radioactivity of 150 to 200 MBq, injected intravenously.

Screening administrations:

To determine tumour uptake at Screening visit, subjects will receive a single i.v. injection of IIP (^{68}Ga-OPS202) administered over 1 minute prior to a PET/CT scan.

EOCT administrations:

To monitor tumour uptake at EOCT visit, subjects will receive a single i.v. injection of IIP (^{68}Ga-OPS202) administered over 1 minute prior to a PET/CT scan.

Investigational Radiopharmaceutical Product (IRPP), ^{177}Lu-OPS201:

The IRPP is a 20-mL solution for infusion with OPS201 dose of either 300 µg (±15%) or 700 µg (±15%) and radioactivity of 3 to 7.4 GBq ^{177}Lu-OPS201. All subject will receive a loading dose ranging from 4.5 to 7.4 GBq (±10%) and a maintenance dose ranging from 3 to 5.5 GBq (±10%), injected intravenously.

***Therapeutic administrations**:*

The IRPP will be administered once per cycle by an i.v. infusion at a rate of 10 mL/h over 120 minutes for ^{177}Lu OPS-201. 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. For renal protection purpose, the IRPP will be co-infused with amino acid solution. The amino acid solution must be administered intravenously over 4 hours (or up to 6 hours in exceptional cases). The infusion of the amino acid solution should start 30 minutes prior to start of IRPP. Premedication with antiemetics should be administered 30 minutes before the start of the amino acid solution. 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.

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

Duration of treatment: ^{177}Lu-OPS201 will be administered once per cycle over a period of two cycles. A treatment cycle is defined as the timeframe of 6 (up to 10) weeks between two administrations or the timeframe of 6 weeks following the last administration. In case of logistical issues, the cycle could be extended by up to additional 2 weeks.

Dosing period can be extended up to 36 weeks in case subjects receive up to four additional cycles.

Reference therapy, dose and mode of administration:

Not applicable.

Criteria for evaluation and Endpoints:

Criteria for evaluation

See Schedule of Assessment in the protocol.

Endpoints

Primary endpoint

Phase I:

The primary endpoint is the MTCA or the MACA if the MTCA is not identified during the phase I. The primary variables determining the MTCA will be the incidence of DLTs and the cumulative organ absorbed doses (Gy) during two cycles of treatment. The DLT assessment period for the determination of the primary endpoint starts from the first administration of ^{177}Lu-OPS201 and ends 6 weeks after the second administration.

Phase II:

The primary endpoint is ORR over the two treatment cycles of the core study measured by the ICL. Objective response is defined as the sum of PR and CR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. All images will be sent to an ICL for evaluation and confirmation of response.

Secondary endpoints

Phase I:

Pharmacokinetics, biodistribution and dosimetry

For PK, biodistribution and dosimetry of ^{177}Lu-OPS201, the endpoints are:

- Maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), maximal uptake (%), area under the curve (AUC) at the target lesions, discernible organs and blood and elimination half-life (t½) of radioactivity concentrations in blood.
- Highest absorbed dose, Specific absorbed dose to the target lesions (Gy/GBq), Specific absorbed dose per organ (Gy/GBq) and Cumulative absorbed organ doses (Gy).

For PK of OPS201, the endpoints are:

- Pharmacokinetic parameters including, but not limited to, C_{max}, AUC, $t_{1/2}$, total plasma clearance (CL), apparent volume of distribution (V_d), cumulative amount (of unchanged drug) excreted into the urine (A_e), renal clearance, as measured in plasma and urine at defined timepoints.

Pharmacodynamic/efficacy

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration compared to Screening as assessed by CT or MRI:
  - RECIST version 1.1 (tumour size is defined as the sum of the diameters of the target lesion in subjects who received ^{177}Lu-OPS201)
  - volumetric CT
- PFS as determined from start of study treatment until occurrence of tumour progression or death.
- BOR defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause.
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
- Changes in tumour uptake (assessed based on SUV_{max} and SUV_{mean}) on ^{68}Ga-OPS202 PET/CT from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle) as compared to clinical response and BOR.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to SOT of ^{177}Lu-OPS201 SPECT/CT.

Phase II:

Efficacy

All the below endpoints will be calculated per cohorts. All imaging endpoints will be assessed by blinded independent readers managed by the ICL.

- Durable response rate (DRR: CR or PR lasting ≥6 months)
- PFS as determined from start of study treatment until occurrence of tumour progression or death.
- Other response endpoints (same timepoints as for PFS):
  - disease control rate (DCR)
  - time to progression (TTP)

- time to response (TTR)
- duration of response (DoR)

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration (each cycle) compared to baseline, as assessed by volumetric CT/MRI.
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause.
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
- Change in ^{68}Ga-OPS202 uptake on PET scan after the second ^{177}Lu-OPS201 administration (second cycle) as assessed by SUV_{max} and SUV_{mean} in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR.
- Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by the identification of avid lesions in subjects screened for ^{177}Lu-OPS201 treatment at baseline.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to SOT of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to SOT of ^{177}Lu-OPS201 SPECT/CT.

Subject Reported Outcomes

- Changes in health-related quality of life scores from baseline to EOCT measured by EuroQoL 5-dimension 5-level (EQ-5D-5L) and The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

Safety Endpoints and Evaluations

- Safety and tolerability measured by the type, nature, severity, expectedness and frequency of AEs overall and per grade according to the current version of the NCI-CTCAE (version 5.0) and significant laboratory abnormalities.

Pharmacokinetics, biodistribution and dosimetry endpoints and measurement timepoints for phase II will be defined according to the phase I results.

Exploratory endpoints

Phase I/II:

Biomarkers

- Association between the uptake on ^{68}Ga-OPS202 PET/CT with sstr2 expression on tumours as determined by IHC.
- Change in renal safety biomarkers compared to baseline.
- Change from baseline in tumour microenvironment, transcriptomics, DNA repair, gene mutations and other disease markers of interest.
- Change from baseline in DNA repair capacity in blood.

Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of additional biomarkers from the biobank samples will be performed outside the scope of the main study and reported separately.

Serum, cfDNA and whole blood ribonucleic acid (RNA) samples will be collected on Day 1 (or Day -1) of Cycle 1, on Day 1 of Cycle 2 and at EOCT or early withdrawal (EW) visit.

Statistical Methods:

Data from phase I and phase II will be analysed and reported separately.

Statistical methodology in phase I

All safety, PK and pharmacodynamics data will be tabulated.

Safety

Continued monitoring of DLTs and toxicities will be performed. At the time of each DRB, the available safety data, including DLTs, toxicities, physiological parameters, ECG, laboratory test results and selected organ absorbed radiation doses (kidney and BM) will be tabulated to guide the radioactivity selection during the dose escalation.

Biodistribution, dosimetry, pharmacokinetics of ^{177}Lu-OPS201

Descriptive summaries of pharmacokinetic parameters, absorbed organ/lesion dose will be presented for each cohort over the treatment period.

Pharmacokinetics of OPS201

If OPS201 levels are measurable in plasma and urine, PK parameters of OPS201 will be derived using a non-compartmental approach. An attempt to build an integrated model taking into account PK, dosimetry, anti-tumour activity and safety data will be made.

Pharmacodynamics of ^{177}Lu-OPS201

Preliminary anti-tumour activity and BOR will be tabulated. Tumour response will be evaluated by the site investigator. Independent review of tumour assessment may be requested at the discretion of the sponsor. In both cases, response and progression will be evaluated using the revised RECIST guidelines and volumetric CT measurement guidance. Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-OPS201 and reached the end of Cycle 2 or EOCT visit will be considered evaluable for response.

Tumour response is assessed locally in the phase I and standardised ceCT/MRI images are collected for the purpose of central reading in case it is requested by health authorities.

Similar analyses to the cohorts with 300 µg (±15%) peptide mass dose will be conducted for the cohorts with the higher peptide mass dose (700 µg (±15%)).

Monitoring of PFS for 2 years after the EOCT Visit (based on RECIST v1.1 status).

Statistical methodology in phase II

Efficacy / Futility analysis

For phase II cohorts, tumour response will be assessed in imaging modalities of CT or MRI scans after 6 weeks of ^{177}Lu-OPS201 administration of Cycles 1 and 2 of the core treatment period and during the 24-month follow-up period every 12 weeks. Images will be reviewed by an independent central review core laboratory. Objective Response Rates and other efficacy parameters will be tabulated. Objective response rate over the two treatment cycles of the core study will be calculated combining the number of subjects with a BOR of confirmed CR or PR per RECIST version 1.1. A similar analysis will be conducted using volumetric CT data.

For the Simon's optimal two-stage design, the hypotheses that will be tested for each cohort are: H_0: $ORR \leq ORR_0$ versus the alternative H_1: $ORR > ORR_0$ where ORR is the true objective response rate following ^{177}Lu-OPS201 treatment that warrants further clinical development, and ORR_0 is the minimum objective response rate to be excluded from further clinical development. The thresholds for ORR and ORR_0 may be updated based on results from phase I and the advances in scientific knowledge.

ORR will be analysed at the end of Stage 1 (6 weeks after the second ^{177}Lu-OPS201 administration (Cycle 2) of the core treatment period of the last evaluable subject of the Stage 1 cohort for each type of cancer). If the observed number of responders is below a predefined threshold, the respective study cohort will be stopped for futility. Otherwise, additional subjects will be treated to complete the planned enrolment. At the end of Stage 2, the null hypothesis will be rejected depending on the total observed number of responders based on a predefined threshold.

At the end of phase II, descriptive summaries will be provided for all primary and secondary efficacy endpoints. For the primary endpoint, final analysis will take into account the sequential sampling procedure of the design and the underlying binomial distribution assumed by the Simon's optimal two-stage design.

Sample size justification (treatment with ^{177}Lu-OPS201)

The sample size in phase II is calculated using Simon's optimal two-stage design based on the ORR rate (CR + PR) following ^{177}Lu-OPS201 treatment.

For the SCLC cohort, with 69 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 23% and an alternative hypothesis ORR rate of 40% at one-sided significance level of α=0.05. The first stage consists of 29 subjects. If seven responses or less are seen in the first 29 subjects then the trial is stopped. Otherwise accrual continues to a total of 69 response evaluable subjects.

For the BC cohort, with 87 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 12% and an alternative hypothesis ORR rate of 25% at one-sided significance level of α=0.05. The first stage consists of 33 subjects. If four responses or less are seen in the first 33 subjects then the trial is stopped. Otherwise accrual continues to a total of 87 response evaluable subjects.

Safety

Descriptive statistics will be calculated for the safety parameters. No formal statistical analyses of safety data are planned.

Biodistribution, radiation dosimetry, PK of ^{177}Lu-OPS201 and OPS201

Analysis will be performed as for phase I and adjusted according to the phase I results.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
A_e	Cumulative amount (of unchanged drug) excreted into the urine
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Immunodeficiency syndrome
ALT	Alanine aminotransferase
AMP	Auxiliary medicinal product
AST	Aspartate amino transferase
AUC	Area under the curve
BC	Breast cancer
BM	Bone marrow
BOR	Best overall response
Bq	Becquerel, SI unit of radioactivity
CA	Competent authority
CDK	Cyclin-dependent kinase
ceCT	Contrast enhanced CT
ceMRI	Contrast enhanced MRI
CI	Confidence interval
CFR	Code of Federal Regulations (United States of America)
CL	Total plasma clearance
C_{max}	Maximum observed concentration
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria Adverse Event
CV	Coefficient of variation
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA-DSB	Deoxyribonucleic acid-double strand breaks
DOM	Dosimetry operational manual

ABBREVIATION	Wording Definition
DoR	Duration of response
DOTA	Tetraxetan (INN), a chemical chelator group
DRB	Data review board
DRR	Durable response rate
EANM	European Association of Nuclear Medicine
EC	Ethic committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED	Extensive disease
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOAC	End of additional cycles
EOCT	End of core trial
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of Study
EQ-5D-5L	EuroQoL 5-dimension 5-level
EU	European Union
EW	Early withdrawal
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GEP-NET	Gastroentero-pancreatic neuroendocrine tumours
GMP	Good Manufacturing Practice
GST	Alpha-glutathione S-transferase
GSTP1	Glutathione S transferase P1
Gy	Gray, SI unit of absorbed radiation dose
HCG	Human chorionic gonadotropin
HEK cells	Human embryonic kidney cells
HER2-	Human epidermal growth factor receptor 2 negative
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography

ABBREVIATION	Wording Definition
HR+	Hormone receptor positive
IAEA	International Atomic Energy Agency
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICL	Imaging core laboratory
IEC	Independent ethics committee
IHC	Immunohistochemistry
IIP	Investigational Imaging Product
IMP	Investigational Medicinal Product
INR	international normalisation ratio
IRB	Institutional review board
IRC	Imaging Review Charter
IRPP	Investigational radiopharmaceutical product
IRR	Infusion related reactions
ISAC	Independent safety assessment committee
ITT	Intent to treat
i.v.	Intravenous
JR11	Somatostatin analogue peptide part (see OPS200)
KIM-1	Kidney injury molecule-1
LD	Limited disease
MACA	Maximum administrable cumulative activity
MCV	Mean corpuscular volume
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mL	Millilitre
mGa-PERCIST	Modified gallium PERCIST
mGA-RECIST	Modified gallium RECIST
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTCA	Maximum administered cumulative activity

ABBREVIATION	Wording Definition
MTSA	Maximum tolerated single activity
MTD	Maximum Tolerated Dose
^{nat}Ga	Naturally occurring gallium, composed of the two stable isotopes ^{69}Ga and ^{71}Ga
^{nat}Lu	Naturally occurring lutetium, composed of one stable isotope ^{175}Lu (97.4% natural abundance) and one long-lived radioisotope ^{176}Lu
NCI	National Cancer Institute
NET	Neuroendocrine tumours
NOAEL	No observed adverse events level
NOS	Not otherwise specified
NSAID	Non-steroidal anti-inflammatory drug
OPS200	Somatostatin analogue peptide part or satoreotide (formally known as JR11)
OPS201	Somatostatin analogue OPS200 coupled to DOTA
OPS202	Somatostatin analogue OPS200 coupled to NODAGA
OPS301	Ipsen's amino acid solution
ORR	Objective response rate
OS	Overall survival
PARP	Poly adenosine diphosphate ribose polymerase
PERCIST	Positron emission tomography response criteria in solid tumours
PET	Positron emission tomography
PFS	Progression free survival
PP	Per protocol
PR	Partial response
PRO	Patient reported outcome
PRRT	Peptide receptor radionuclide therapy
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
QC	Quality control
QoL	Quality of life
RBC	Red blood cell(s)

ABBREVIATION	Wording Definition
RECIST	Response evaluation criteria in solid tumours
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SCLC	Small cell lung cancer
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SoC	Standard-of-care
SOC	System organ class
SOP	Standard Operating Procedure
SOT	Standard-of-truth
SPECT	Single Photon Emission CT
sstr2	Somatostatin receptors subtype 2
SUL	SUV normalised by lean body mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake volume
$t_{½}$	Elimination half life
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum observed concentration
TSH	Thyroid stimulating hormone
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
USA	United States of America
V_d	Apparent volume of distribution
WBC	White blood cell(s)
WHO-DD	World Health Organisation-Drug Dictionary
µg	Microgram
^{68}Ga	Gallium-68, positron-emitting isotope of gallium
^{68}Ga-OPS202	Study medication; ^{68}Ga-radiolabelled somatostatin analogue for diagnostic imaging
^{111}In	Indium-111, gamma-emitting isotope of indium

ABBREVIATION	Wording Definition
^{177}Lu	Lutetium-177, beta- and gamma-emitting isotope of lutetium
^{177}Lu-OPS201	Study medication; ^{177}Lu-radiolabelled somatostatin analogue for PRRT

1 BACKGROUND INFORMATION

As part of Ipsen's peptide receptor radionuclide therapy (PRRT) development program, ^{177}Lu-OPS201, a radiolabelled compound targeting the somatostatin receptor subtype 2 (sstr2), is currently being developed in Grade 1 and 2 gastroentero-pancreatic neuroendocrine tumours (GEP-NET). These tumours are indeed known to show high expression of the sstr2 subtype at the cell surface (Kaemmerer 2015).

Somatostatin binds to all of the sstrs without preference, but the result of somatostatin binding appears to be receptor specific as well as organ dependent, though there is some overlap between the different receptor subtypes. Somatostatin has several downstream effects, including on cellular secretion, motility, and even proliferation. It has a major endocrine "off switch" function including control of hormone secretion with significant antiproliferative properties, having both autocrine and paracrine activity. Sstrs modulate several key enzymes involved in the cell cycle, including inhibition of adenylate cyclase, impairment of calcium influx, increasing p53 expression and Bax to initiate apoptosis, and affecting ERK1/2 and AKT to decrease cell proliferation. Therefore, sstrs play not only a major role in normal human biology, but also have a key role in cancer biology.

CCI [redacted]

1.1 Introduction

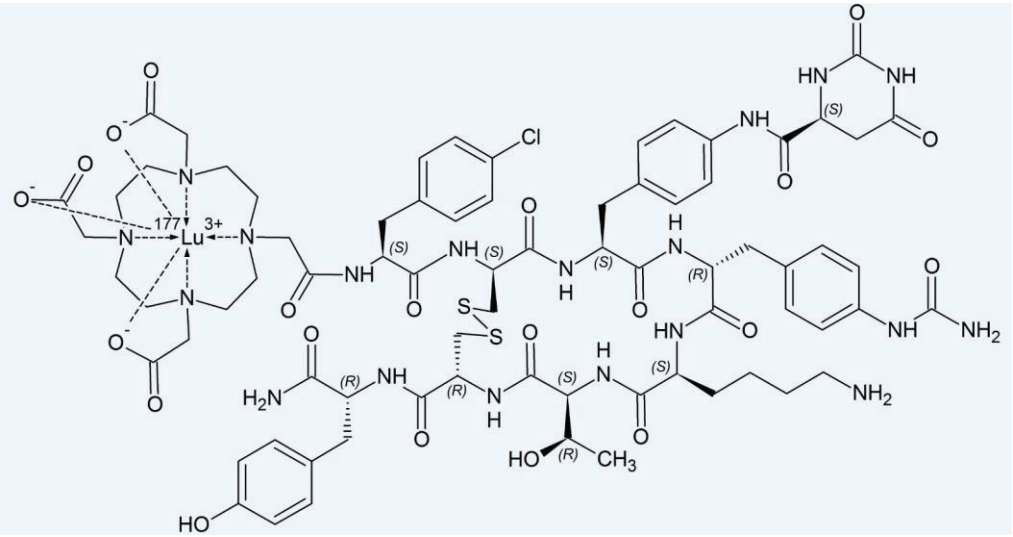
This phase I/II study will expand the emerging data from NET phase I studies (Wild 2014, Reidy 2017) and will be the first study aiming to guide the administration of ^{177}Lu-OPS201 through subject selection based on ^{68}Ga-OPS202 PET/CT in a population with a different benefit-risk profile (subjects with non-NET sstr2-positive tumours) under controlled study conditions. The aim of the phase I will be to evaluate the safety and the recommended treatment schedule of ^{177}Lu-OPS201 as well as to assess the first evidence of anti-tumour activity in non-NET sstr2-positive tumours as identified by ^{68}Ga-OPS202 PET/CT. Phase II will confirm the safety and evaluate the efficacy of ^{177}Lu-OPS201 in non-NET sstr2-positive tumours and will be conducted according to an adaptive design. In both phase I and phase II, ^{68}Ga-OPS202 will be used for PET scans for the screening of subjects to identify those with an uptake in the tumour superior to uptake in non-tumoural liver tissue. In this study, ^{68}Ga-OPS202 will also be evaluated as a surrogate endpoint for the response to ^{177}Lu-OPS201 therapy.

1.2 Name and Description of Investigational Imaging/Medicinal Products

^{68}Ga-OPS202 (satoreotide trizoxetan) is an imaging compound which consists of a somatostatin analogue peptide moiety (OPS200, formally known as JR11) conjugated to the strong macrocyclic chelating agent NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid), which is radiolabelled with the radioactive isotope gallium-68 (^{68}Ga). The compound ^{68}Ga-OPS202 is being developed as a PET imaging agent for the detection of sstr2-positive tumours in subjects.

^{177}Lu-OPS201 (satoreotide tetraxetan) is a drug substance consisting of three main components, namely the same OPS200, linked to the macrocyclic chelator DOTA (1,4,7,10 tetraazacyclododecane-1,4,7,10-tetraacetic acid) which chelates the beta emitter lutetium-177 (^{177}Lu) radioisotope (see Figure 1). It is used for therapeutic application.

Figure 1 Chemical structure of the radiopharmaceutical product ^{177}Lu-OPS201



A more detailed description of the product is given in Section 3.6.

1.3 Auxiliary Medicinal Product

An amino acid solution, consisting of arginine and lysine, will be co-infused as an auxiliary medicinal product (AMP) with ^{177}Lu-OPS201. Its role is to prevent nephrotoxicity during PRRT by blocking ^{177}Lu-OPS201 reabsorption. The joint International Atomic Energy Agency (IAEA), the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) practical guidance on PRRT in NETs (Bodei 2013) recommends for renal protection to infuse a solution containing a 50-g cocktail of lysine and arginine (25 g of lysine and 25 g of arginine) diluted in 2 L. The solution should be infused over 4 hours, starting 30 to 60 minutes before ^{177}Lu-OPS201 administration (see more details in Section 6.3.1).

Sites experienced in PRRT treatment can use Ipsen's amino acid solution (OPS301, which will be provided during the study) or their established amino acid solution, preferably from commercial source, if it is covered by the recommendations of the joint IAEA, EANM and SNMMI practical guidance on PRRT in NETs (Zaknun 2013). The exact formulation and source must be documented in the eCRF.

1.4 Findings from Nonclinical Studies

1.4.1 In Vitro Pharmacology

1.4.1.1 ^{68}Ga-OPS202

Receptor binding affinities of OPS202 and ^{nat}Ga-OPS202 were analysed in sstr2 overexpressing human embryonic kidney (HEK) cells. The metal ion in the chelator cage positively influenced the receptor binding affinity of the peptide (Fani 2012). The peptide antagonist ^{nat}Ga OPS202 showed slightly weaker affinity to the sstr2 (half maximal inhibitory concentration (IC_{50}) 1.2±0.2 nM) compared to the peptide agonist ^{nat}Ga-DOTATATE (IC_{50} 0.2±0.04 nM). In saturation experiments, ^{67}Ga-OPS202 demonstrated ability to bind 4- to 6-fold more sites using

transfected sstr2 cell line as compared to ^{67}Ga-DOTATATE or ^{67}Ga-DOTATOC respectively [Data on file, IPSEN].

Internalization studies based on immunofluorescence microscopy were performed on sstr2 expressing HEK cells to determine the functional behaviour of the somatostatin analogue OPS202. To do so, the chelator-conjugated peptide was labelled with ^{nat}Ga (^{nat}Ga OPS202) and compared to ^{nat}Ga-DOTATOC, which is known to be a receptor agonist. Clear punctate perinuclear staining was detectable after treatment of HEK cells with ^{nat}Ga-DOTATOC. ^{nat}Ga-OPS202 in the presence of ^{nat}Ga-DOTATOC did not induce receptor internalization and was thereby proven to be a receptor antagonist (Fani 2012).

1.4.1.2 ^{177}Lu-OPS201

Different in vitro pharmacology tests were performed using transfected cell lines over-expressing the somatostatin receptors, or NCI-H69 known to express sstr2 (cell membranes for saturation and competition, or entire cells for internalization or calcium assay). In saturation experiments, ^{177}Lu-OPS201 demonstrated high affinity to sstr2 (0.07 nM) and ability to bind 2- to 4-fold more sites using NCI-H69 or transfected sstr2 cell line respectively as compared to ^{177}Lu-DOTATATE [Data on file, IPSEN].

OPS201 in competition experience displayed high selectivity to other somatostatin receptor subtypes (1, 3, 4 and 5) with $IC_{50} > 1000$ nM (Fani 2012).

An internalization assay based on sstr2 immunofluorescence microscopy with sstr2 overexpressing HEK cells was performed to determine whether OPS201 (compound 31 in Cescato 2008) works as an agonist or antagonist. In comparison to the control analogue TOC, OPS201 alone and in the presence of agonist TOC did not induce internalisation of sstr2. Furthermore, unlike in the presence of the agonist it did not activate calcium signalling in a calcium release assay and therefore acts as a receptor antagonist (Cescato 2008).

1.4.2 In Vivo Pharmacology

^{177}Lu-OPS201 demonstrated its potency to reduce tumour growth in one animal model NCI-H69 xenograft in mice (small cell lung cancer (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-DOTATATE, or 200 mL of injection fluid. Animals treated with ^{177}Lu-OPS201 showed a decrease in tumour size up to 45±7 days after injection after which tumour regrowth occurred. For ^{177}Lu-DOTATATE, 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-DOTATATE group and the ^{177}Lu-OPS201 treated group, respectively (Dalm 2016a).

1.4.3 Toxicology

1.4.3.1 ^{68}Ga-OPS202

OPS202 and ^{nat}Ga-OPS202 showed high specificity to the targeted sstr2 in a binding profile in vitro assay, indicating low risk for off-target effects [Study no. CCI]. Safety pharmacology studies did not show any potential safety effect [Studies no. CCI . In extended single-dose rat [Study no. CCI] and minipig [Study no CCI] toxicology studies using intravenous administration, OPS202 did not show relevant toxicological effects at high safety margins (at least 308 times the human equivalent dose of 45 µg in human).

1.4.3.2 ^{177}Lu-OPS201

OPS201 and ^{nat}Lu-OPS201 showed high specificity to the targeted sstr2 in a binding profile in vitro assay, indicating low risk for off-target effects [Study no. CCI . To investigate the safety profile of the clinical formulation intended for patients, ^{nat}Lu-OPS201 in OPS201 was tested in a single dose minipig study [Study no. CCI and repeated dose rat [Studies no. CCI and CCI] studies using intravenous administration. No adverse effect has been observed in all investigated parameters of the treated animals. Transient clinical signs in minipigs (redness, decreased activity and vomiting immediately after administration) and renal findings in rats, both considered as non-adverse, were noted at high safety margins (at least 255 times the human equivalent dose of 300 µg in human and approximately 106 times the human equivalent dose of 700 µg in human). Safety pharmacology investigations and genotoxicity studies [Studies no. CCI , CCI and CCI did not show any potential safety effect.

1.4.4 Pharmacokinetic Properties of Unlabelled OPS201

Pharmacokinetic and toxicokinetic studies have been performed in Sprague Dawley rats after single and repeated intravenous administration of ^{nat}Lu-OPS201 in OPS201. Pharmacokinetic profiles were similar between ^{nat}Lu-OPS201 and OPS201, with short elimination half-life (1 to 3 hours), low plasma clearance and low volume of distribution. Linearity across the tested dose range and lack of apparent accumulation of OPS201 and ^{nat}Lu-OPS201 were observed after repeated administrations [IPSEN Report no. CCI and CCI]. Similar pharmacokinetic profile was observed in Gottingen Pig after single intravenous administration of ^{nat}Lu-OPS201 in OPS201 [IPSEN Report no. CCI , CCI].

1.4.5 Biodistribution and Dosimetry of Radiolabelled ^{177}Lu-OPS201

A biodistribution study of ^{177}Lu-OPS201 was investigated in mice bearing sstr2 expressing tumours (HEK human sstr2) at different injected doses of peptide mass (10, 200 and 2000 pmol) (Nicolas 2017). ^{177}Lu-OPS201 accumulated predominantly in sstr2 expressing tumours and in the receptor positive organs such as pancreas, stomach and adrenals. A relatively high accumulation was found in the kidneys, as a consequence of urinary excretion. ^{177}Lu-OPS201 exhibits a higher tumour uptake and a longer tumour residence time compared with ^{177}Lu-DOTATATE. The mean tumour residence time was 15.6 hours for ^{177}Lu-OPS201 and 6.4 hours for ^{177}Lu-DOTATATE, based on non–decay-corrected biodistribution data and normalised per gram of tumour. The different injected doses of peptide mass (10, 200 and 2000 pmol, respectively) did not affect significantly the tumour uptake and the tumour-to-kidney ratio. On the other hand, the injected peptide dose had a major effect on the uptake of the other organs (i.e. tumour-to-liver from 16 to 80 and tumour to bone marrow (BM) from 25 to 150, from 10 to 2000 pmol, at 4 hours post-injection). The increased mass dose improved the tumour-to-bone marrow uptake ratio suggesting a favourable dosimetry profile at higher mass dose.

Tissue distribution of ^{177}Lu-OPS201 was also evaluated in sstr2 expressing tumour bearing mice (human small cell lung cancer H69) at peptide doses of 0.5 µg (300 pmol), 1 µg (600 pmol) and 2 µg (1200 pmol) (Dalm 2016a). 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 absorbed 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.

A dosimetry study with ^{177}Lu-OPS201 was also conducted in six Danish Landrace pigs. ^{177}Lu-OPS201 was well tolerated and produced no abnormal physiological or behavioural signs. The amino acid solution, however, induced a strong physiological response in two of the six animals: The first animal's breathing became very difficult and it urinated twice the volume usually observed. The amino acid infusion was stopped and the pig was given saline and glucose to stabilise it. However, the second animal could not be stabilised and was euthanised before dosing with ^{177}Lu-OPS201 (IPSEN report no. [redacted]).

Ultimately, the dosimetry study was performed in five pigs co-treated with an amino acid solution for kidney protection (except for pig no. 5). The highest absorbed dose coefficients were observed in the kidneys (2.73 mGy/MBq), the osteogenic cells (0.79 mGy/MBq), the urinary bladder wall (0.35 mGy/MBq) and the liver (0.20 mGy/MBq). Based on the results of this study, the amino acid infusion plays an essential role for kidney protection. According to the data of Pig number 5, the lack of amino acid infusion may result in a two-fold increase of the absorbed dose to the kidney (Beykan 2016, Lassmann 2008).

In humans, the organs expected to show the highest exposure are the kidneys, the osteogenic cells, the urinary bladder wall and the liver. For an injection of 7.5 GBq (giga-becquerels), none of the predicted absorbed doses exceeded toxicity levels, particularly in red marrow (1.14 Gy) and kidney (20.6 Gy). Of note, 2 Gy and 23 Gy are commonly considered as upper safety limits for the red marrow and kidney absorbed doses (Verburg 2013, Rolleman 2010). The known and potential risk of radiation organ toxicity is outlined in Section 1.6.

1.5 Findings from Clinical Studies

1.5.1 ^{68}Ga-OPS202

1.5.1.1 Compassionate Use in NET Subjects

PPD

PPD

These imaging results confirmed the expectation of ^{68}Ga-OPS202 being an adequate radiopharmaceutical tracer and potentially superior to Octreoscan® or the more recently studied ^{68}Ga-DOTATOC in the diagnosis of GEP-NET lesions (OPS202 Investigator Brochure).

1.5.1.2 Study OPS-B-001 in GEP-NET Subjects

A single-centre, open-label, dose-finding, single-dosing study (Study OPS-B-001) was conducted to evaluate safety and tolerability, as well as biodistribution, dosimetry and preliminary efficacy of two single ^{68}Ga-OPS202 peptide mass doses (15±5 and 50±15) µg, each labelled with the same radioactivity of 200 MBq ±25% ^{68}Ga tracer (as initially described in the

study protocol) for the diagnostic imaging of sstr2-positive GEP-NET using PET/CT (Nicolas 2017).

Six out of 12 subjects (50.0%) experienced 11 adverse events (AEs), all of which were assessed by the investigator as being non-serious. Most of the AEs were mild in intensity and were considered by the investigator as unlikely or not related to the Investigational Imaging Product (IIP). Three AEs (all Grade 1) in two subjects were assessed as possibly related to ^{68}Ga-OPS202: eosinophilia, rash and diarrhoea. At the end of the study, rash and diarrhoea were reported as resolved.

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

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

1.5.2 ^{177}Lu-OPS201

1.5.2.1 Investigator Sponsored Pilot Study in NET Subjects

The investigational radiopharmaceutical product (IRPP), ^{177}Lu-OPS201, has already been used in a pilot therapeutic study at the University Hospital in Freiburg (Wild 2014).

This study included four subjects with histologically proven, progressively metastasised inoperable NETs and limited treatment options due to chronic Grade 2 or 3 kidney disease. These subjects received test injections of ^{177}Lu-OPS201 (150±20 µg, 975±115 MBq) and ^{177}Lu-DOTATATE (175±15 µg, 1060±75 MBq) and then two to three therapeutic cycles of ^{177}Lu-OPS201 (105±35 µg, 4.12±1.26 GBq per cycle) with dosing interval of 8 weeks. The IRPP (^{177}Lu-OPS201) showed significantly longer intratumoural residence time and higher tumour uptake than ^{177}Lu-DOTATATE in all four subjects (between 1.3 and 2.8 times longer residence time and between 1.1 and 2.6 times higher tumour uptake), resulting in a 1.7 to 10.6 times higher tumour dose. The median tumour dose was 7.0 Gy/GBq with ^{177}Lu-OPS201 versus 2.0 Gy/GBq with ^{177}Lu-DOTATATE. Tumour-to-kidney and tumour-to-bone marrow dose ratios were up to 6.2 and 7.2 times higher for ^{177}Lu-OPS201 than for ^{177}Lu-DOTATATE. Reversible minor adverse effects of ^{177}Lu-OPS201 were observed. All subjects developed reversible Grade 1/2 of leukopenia and/or anaemia and one subject Grade 3 thrombocytopenia, which completely recovered within 8 weeks after injection of ^{177}Lu-OPS201 (Table 1). Despite the unfavourable initial tumour stage of the subjects, the treatment resulted in partial response in two subjects, stable disease in one subject and mixed response in the fourth subject after a 12 to 15-month follow-up.

Table 2 Number of ^{177}Lu-OPS201 treatment cycles, cumulative radioactivity and safety data per subject

Subject number	Treatment cycle number	Interval between cycles (weeks)	Cumulative injected radioactivity (GBq)	Haematotoxicity Grade (highest)		BM cum dose (Gy)[a]	Kidney cum dose (Gy)
				WBC	Platelets		
1	2	8	6.1	2	0	0.79	13.66
2	3	8	15.2	1	3	1.50	22.34
3	2	8	5.9	2	0	0.55	8.437
4	3	8	13.7	0	0	1.12	29.46

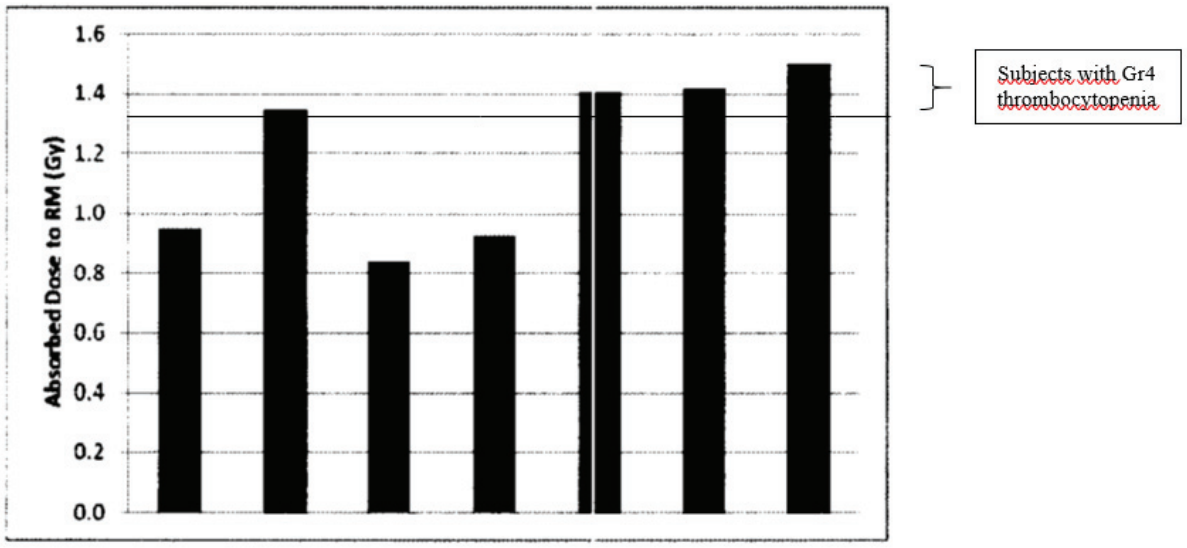
Source: Wild 2014
Abbreviations: GBq=gigabequerels; Gy=gray; WBC=white blood cell count.
a BM cum dose: cumulative bone marrow dose (determined by blood-based red-marrow dose methodology).

1.5.2.2 Investigator Sponsored Study in NET Subjects

An investigator study sponsored by Memorial Sloan Kettering Cancer Center (MSKCC), New York, United States of America (USA) was also initiated (Reidy 2017, NCT02609737). A total of 19 subjects (52% female) with heavily treated NETs and average age of 55 years (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 absorbed 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 contained up to 100 µg peptide (Data on file).

Seven subjects received two therapeutic cycles of ^{177}Lu-OPS201 with cumulative activities ranging from 13.28 to 16.65 GBq and the other 12 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 five subjects (26%) exhibited Grade 3 leukopenia that reversed to Grade 1 or Grade 0 before the second cycle. By contrast, 4/7 subjects were noted to have Grade 4 haematological toxicities (four thrombocytopenia and one leukopenia) starting 4 to 6 weeks after the administration of ^{177}Lu-OPS201 after the second cycle. These Grade 4 toxicities were long lasting and resolved to Grade 2 or lower in more than 8 weeks; none of these subjects demonstrated fever, infection, bleeding, or renal toxicity. The mean relative BM absorbed dose (image-based method) was 0.077 Gy/GBq (range: 0.049 to 0.11) and the individual BM absorbed doses ranged from 1.3 to 1.5 Gy in subjects who showed severe thrombocytopenia whereas it was below 1 Gy in the other subjects (Figure 2).

Figure 2 Individual Bone Marrow Absorbed Doses in Subjects Who Received Two Therapeutic Cycles (n=7; image-based method)



Source: Data on file

Following these safety events, the study was put on clinical hold and an amendment was prepared to reduce the limiting BM absorbed dose to 1 Gy and reduce the administered cumulative radioactivity so that the study has now restarted.

The median tumour absorbed dose in the study was about 7.2 Gy/GBq. Preliminary efficacy results indicate that one subject had a complete response (5%), six a partial response (32%), nine stable disease (47%) and three disease progression (16%). Among the seven subjects having received the two therapeutic cycles (13.28-16.65 GBq), one subject had a complete response (14%), three a partial response (43%), two a stable disease (29%) and one disease progression (14%) (Reidy 2017 and Data on file).

Further details may be found in the Investigator's brochure (IB).

1.5.2.3 Ipsen Sponsored Study in NET Subjects

A study sponsored by Ipsen (study OPS-C-001) has also been initiated. A total of 27 subjects with heavily treated NETs have been included in this study (27 February 2019). The study, currently ongoing in Europe, is split into two parts. For Part A, for each treatment cycle, subjects received approximately 4.5 GBq of ^{177}Lu-OPS201 at a peptide mass of approximately 300 µg. Part B is a dose escalation cohort design evaluating both peptide mass and radioactivity dose.

A safety review committee was held after the first six subjects completed their third administration. Only two serious adverse events were reported: one Grade 3 drug-related vaso-vagal reaction and one Grade 3 unrelated fever. One Grade 2 and one Grade 3 thrombocytopenia events were both seen in one subject. In the other subjects, only mild reversible thrombocytopenia and anaemia events as well as non-clinically significant lymphopenia events were observed. Short-lived reversible infusion-related episodes of different severity were managed successfully with infusion rate modification in three subjects. One subject was unable to receive the full dose (30%). Regarding anti-tumour activity, three subjects had confirmed partial response, one subject had unconfirmed partial response and five subjects had stable disease. Please refer to the IB for further safety information.

1.6 Known and Potential Risks and Benefits to Human Subjects

The therapeutic antagonist compound itself (^{177}Lu-OPS201) and related agonist compounds (^{177}Lu-DOTATATE) have already demonstrated anti-tumour activity in Grade 1 and 2 GEP-NET that are known to overexpress sstr2 (Reidy 2017, Strosberg 2017). Moreover, in a preclinical model (NCI-H69) with a level of sstr2 expression in the same range of some SCLC biopsy samples, ^{177}Lu-OPS201 presented a potential competitive advantage due to its specific binding properties as compared to ^{177}Lu-DOTATATE and demonstrated higher uptake and inhibition of tumour growth.

Based on this clinical and non-clinical evidence and since the target tumour types of this study (extensive disease (ED)-SCLC and hormone receptor positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer (BC)) have also shown significant expression of sstr2, evaluating ^{177}Lu-OPS201 in these populations is justified.

Subjects whose tumour have adequate level of sstr2 expression and consequently would have potential benefit with ^{177}Lu-OPS201 treatment will be first selected with the companion diagnostic imaging product. The compound ^{177}Lu-OPS201 and its imaging companion may thus offer a treatment option beyond standard of care for cancers such as progressing or refractory advanced SCLC and metastatic HR+ HER2-BC for which the unmet clinical and therapeutic needs are high.

^{68}Ga-OPS202 will be administered at the micro dosing ranges and PET/CT images will be acquired at the time defined by the data generated in GEP-NET subjects. The novel PET sstr2 ligand ^{68}Ga-OPS202 performance in low sstr2 expressing tumours is currently explored and evaluated. It is possible that due to tumour heterogeneity, small lesion sizes and low receptor density, the avidity required on ^{68}Ga-OPS202 PET/CT scans during the screening period would not be met, resulting in an important screening failure in the identification of subjects to be treated with ^{177}Lu-OPS201.

It is hypothesised that a significant sstr2 expression level in a tumour lesion will correspond to a positive ^{68}Ga-OPS202 PET imaging according to the criteria requested for enrollment. Significant sstr2 expression corresponds to tumour lesion with at least moderate H score (≥50), as assessed by Immunohistochemistry (IHC). Internal IHC studies demonstrated a significant expression of sstr2 in 15% of HR+/HER2- BC and SCLC samples tested. Therefore, it is anticipated to assess positive PET imaging results with ^{68}Ga-OPS202 for at least 15% of subjects. As there is uncertainty with regards to the in-vivo characterisation of the sstr2 overexpression in the tumour types targeted in this study and in order avoid exposing an important number of subjects to ^{68}Ga-OPS202, a futility criterion is defined. Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with less than one subject deemed sstr2-positive while all the other inclusion/exclusion criteria are met, the administration of ^{68}Ga-OPS202 and subsequent PET imaging will be stopped.

An additional eligibility criterion for ^{177}Lu-OPS201 administration requires radiologically ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reading (inclusion criteria #11). Some of the malignant lesions might show low or no metabolism on ^{18}F-FDG-PET/CT and low or no focal uptake of ^{68}Ga-OPS202 on PET. However, sstr2 expression might also be heterogenous, thereby leading to high retention of FDG with no uptake for ^{68}Ga-OPS202 for some of the malignant lesions. The rationale for ≥50% matching of the two PET radionuclides is to ensure there is sufficient tumour burden that is sstr2-positive to ensure the possibility of a good response with ^{177}Lu-OPS201.

There were no major safety concerns reported during the previous and ongoing studies conducted with ^{68}Ga-OPS202.

The known and potential risk to human subjects with ^{177}Lu-OPS201 as for all radiopharmaceuticals is the occurrence of haematotoxicity, particularly high-grade thrombocytopenia according to the administered and cumulative radioactivity. This risk will be mitigated by setting specific inclusion criteria in terms of estimated haematological reserve (e.g. platelet count level at baseline greater than currently recommended level) and monitoring haematology once a week after each administration of ^{177}Lu-OPS201. Moreover, dosimetry will be performed up to 168 hours after each treatment cycle to carefully evaluate the BM absorbed dose. A maximum absorbed dose of 2 Gy to the BM is generally accepted (ICRP Publication 128) with a probability for developing leukaemia of approximately 2%. In this study, the maximum absorbed dose in BM has been decreased to 1.5 Gy considering the safety results of MSKCC study. In MSKCC study, subjects with BM absorbed dose greater than 1.3 to 1.4 Gy indeed showed Grade 4 thrombocytopenia. The limit was nevertheless set to 1.5 Gy since the limit in maximum absorbed dose to the BM is a precaution to minimise longer term risks, such as leukaemia rather than to prevent acute haematotoxicities and since a limit of 1 Gy would limit too much the administered cumulative radioactivity. Moreover, the precision of the absorbed dose evaluation will be optimised by using an imaged-based method for computation of BM absorbed dose (Hindorf 2010) as well as by using Single Photon Emission Computerised Tomography (SPECT)/CT rather than planar scintigraphy for dosimetry analysis.
In addition, the peptide doses administered (300 µg or 700 µg (±15%)) will be at least 3-times higher than in the MSKCC-sponsored trial (<100 µg). Based on pre-clinical data (mouse model, see Section 1.4.5), the highest peptide dose (cold peptide) is thought to increase tumour-to-background ratio and thus to improve safety by saturating sstr2 receptors in non-target organs (like BM) but not in the tumour. The proportion of hot peptide is about 1 to 3% of the total peptide mass and thus at least 97% of the administered peptide mass is cold. Therefore, with increasing peptide mass, receptor saturation mostly with cold peptide is expected in organs such as the BM, whereas in the tumour, where sstr2 is overexpressed, receptor saturation is unlikely, leading to a higher peptide concentration and hence more radioactivity. This should further improve the tumour-to-background ratio of hot to cold peptide.

Another potential risk with such compound is nephrotoxicity. Proximal tubular reabsorption of the radiopeptide and subsequent retention in the interstitium result in excessive and sustained renal irradiation. This risk will be mitigated by specific renal function inclusion criterion (estimated glomerular filtration rate (eGFR)>55 mL/minute) and infusion of amino acid solution (as OPS301) concomitant to ^{177}Lu-OPS201 administration. The amino acid solution, consisting of the positively charged amino acids L-lysine and L-arginine, reduces tubular reabsorption of ^{177}Lu-OPS201 by saturating renal transporters.

Subjects will be carefully selected using ^{68}Ga-OPS202 (sstr2) imaging to avoid administration of ^{177}Lu-OPS201 to subjects with tumours with inadequate levels of sstr2 expression who consequently would not have potential benefit.

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 (ICRP Publication 128). In the urinary bladder wall and liver, the estimated absorbed doses (4.8 and 4.3 Gy, respectively) at the anticipated highest cumulative administered activity (7.4+5.5=12.9 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) (ICRP Publication 41).

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 (Kaushansky 2009, Bakovic 2005, Spencer 1975). It is reported to be the organ that receives the highest mean absorbed dose of all organs during PRRT (Bodei 2011, Kwekkeboom 2001), partly because of the presence of somatostatin receptors on lymphocytes (Reubi 1990, Wehrmann 2007). A dose-dependent relationship may exist between the total absorbed dose to the spleen and the blood cell count (Sabet 2013). In the spleen, the estimated absorbed dose is 38.7 Gy at the anticipated highest administered activity (7.4+5.5=12.9 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 (Teunissen 2009, Zatelli 2004, Baou 2000). Therefore, it is not unlikely that subjects treated with PRRT 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 at end of 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 (Wild 2014). The exception is the ovaries, where the radiation dose limit is 2-3 Gy (over this limit, there is a risk of permanent sterilization). With a specific absorbed dose of 0.1 Gy/GBq, absorbed doses of about 1.3 Gy could be reached at the highest administered activity (12.9 GBq).

Participating subjects will be carefully monitored up to Day 3 in the morning and then will come back every week for AEs, laboratory tests, etc. They may be hospitalised until Day 3. 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. Each additional administration will be based on individual safety and tolerability. No ^{177}Lu-OPS201 will be administered to subjects who did not tolerate previous administration or did exceed the maximum organ radiation absorbed dose.

Additional information regarding risks and benefits to human subjects may be found in the IB.

1.7 Selection of Investigational Radiopharmaceutical Products and Dosages

1.7.1 ^{68}Ga-OPS202

In the pre-treatment period, all subjects with the informed consent signed will receive a single iv dose of ^{68}Ga-OPS202, consisting of a peptide mass up to 45 µg, with a radioactivity range of 150-200 MBq radioactivity of ^{68}Ga. ^{68}Ga-OPS202 will be prepared up to 3 hours prior to administration by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit containing 50 µg of peptide.

The PET images will be acquired at 1-hour post injection and one contrast enhanced (ce) CT scan will be acquired. The peptide mass and radioactivity range are based on findings from preclinical and clinical data in subjects with GEP-NET sstr2-positive. All images will be sent to an imaging core laboratory (ICL) for blinded reading. ^{68}Ga-OPS202 uptake in target tissue (primary tumour, lymph nodes and/or metastases) will have to show at least two avid lesions of ≥20 mm on longest diameter with 1.5-fold or greater uptake than the non-tumour liver and lung tissue on PET/CT. Radiologically, ≥50% matching between the lesions detected on

^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reading will be required for enrolment.

Dosing of ^{68}Ga-OPS202 and PET image acquisition time as well as the eligibility criteria for sstr2 positivity could be revised at the start of phase II should emerging data from phase I and ongoing studies support modifications specific to these sstr2 expressing tumours.

Note: an application for a substantial amendment will be submitted for approval by the Competent Authorities (CAs) and/or Ethic Committees (ECs) (as applicable) before initiating changes to the study conduct.

Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with less than one subject having at least two avid lesions of ≥20 mm on longest diameter with 1.5-fold or greater uptake than the non-tumour liver and lung tissue on PET/CT while the other inclusion/exclusion criteria met, the administration of ^{68}Ga-OPS202 and subsequent PET imaging will be stopped. Selection of sstr2-positive tumours for the treatment with ^{177}Lu-OPS201 will be revised in a protocol amendment.

1.7.2 ^{177}Lu-OPS201

The cumulative radioactivity range (9 to 12.9 GBq) applied in this study is derived mainly from previous experiences with ^{177}Lu-OPS201 in subjects with NET (See Section 1.5.2). A statistical model correlating radioactivity and dose limiting toxicities (DLTs) as well as radioactivity and thrombocytopenia incidence from NET data also supported the choice of the maximum tolerated cumulative radioactivity and the possible starting radioactivity.

1.7.2.1 Treatment Schedule

In this phase I radioactivity escalation, the radioactivity will be administered fractionated into one loading dose and one lower maintenance dose (e.g. 6 GBq followed by 3 GBq). The treatment schedule differs from the flat-dosing proposed for NET subjects in which sstr2 expression reaches almost 100% and for whom the natural disease course is longer. With the aim to obtain a sufficient tumour absorbed dose in low expressing sstr2 tumours to translate into initial shrinkage of the lesions, the principle of intensive chemotherapy has been proposed in the current study. The schedule with a loading radioactivity is supported by the need for prompt effect on tumour bulk (decrease or stabilization), due to tumour doubling time and short life expectancy/fast clinical deterioration of the subject. The maintenance radioactivity should aim to prevent that doubling time growth take over again while ensuring a balanced benefit-risk ratio. As achieved tumour doses play an important role in treatment efficacy (Strigari 2014), the dosing regimen may need to be adapted to the tumour type and stage of the disease. Dose-intensity is equally important, the rhythm and dosage of cures are also calculated according to the recovery time and, in this case, in order to avoid dose-limiting haematological toxicity. In this context, we hypothesise that this dose-intensified regimen, with a loading dose with the highest single tolerated radioactivity followed by maintenance dose(s) (optimal lower radioactivity) would yield better benefit risk ratio comparing to a flat-dosing regimen and thus provide a therapeutic opportunity to these patients.

1.7.2.2 Dosing Interval of ^{177}Lu-OPS201

In radiotherapy, fractionation of the cumulative radioactivity is done for safety and tolerability reasons. However, the number of administrations (two cycles for DLT assessment) and the interval between two administrations (6 weeks) in this study have been reduced compared to NET subjects who receive three cycles separated by 8 weeks. Indeed, in this new target patient populations (e.g. ED-SCLC, pre-treated HR+ HER2- metastatic BC), tumour progression is rapid and may not allow to keep an 8-week interval between two administrations. The choice

of the dosing interval was driven by safety data rather than pharmacokinetic data, as the elimination of ^{177}Lu-OPS201 is quick. Indeed, based on whole body scans acquired over 144 to 168 hours after the start of the ^{177}Lu-OPS201 administration, the mean remaining activity in the whole body is below 15% after 144 hours. Regarding safety data, the nadir of the blood cell counts decrease (any grade) occurred between 4 and 6 weeks after ^{177}Lu-OPS201 administration, as shown in MSKCC study (Reidy 2017, NCT02609737). These findings seem to be confirmed by the results of the ongoing Ipsen sponsored OPS-C-001 study in NET. The mean time to nadir of the platelet count (any grade) in this study was indeed 29 days after Cycle 1 (n=10), 32 days after Cycle 2 (n=5) and up to 46 days after Cycle 3 (n=5). The interval of 6 weeks was thus chosen since it allows to both reduce the risk of progression before the second administration and leave enough time to detect any potential haematotoxicity arising after each administration of ^{177}Lu-OPS201. Moreover, the protocol offers the possibility to extend the dosing interval by up to 4 weeks if a subject has not recovered from a >Grade 1 thrombocytopenia, anaemia or neutropenia. In any case, only subjects with adequate haematological reserve (defined as: white blood cells (WBC) ≥3000/µL, with absolute neutrophil count ≥1000/µL, platelet ≥100,000/µL and red blood cell (RBC) ≥3x10^6/µL) can be considered to receive an administration of ^{177}Lu-OPS201.

1.7.2.3 Starting Cumulative Radioactivity of ^{177}Lu-OPS201

In this study, 9 GBq fractionated in two administrations (6 GBq followed by 3 GBq) will be used as the starting cumulative radioactivity. Indeed, the previous studies in NET showed good tolerance in this range of radioactivity. In the first in human pilot study performed in four subjects with advanced NET (Wild 2014), two cycles of 4.12 ± 1.26 GBq were well tolerated and three cycles showed encouraging preliminary anti-tumour activity. This treatment led to organ absorbed doses of 0.10 ± 0.021 Gy/GBq in BM (i.e. about 0.9 Gy for a cumulative radioactivity of 9 GBq) and 1.8 ± 0.44 Gy/GBq in kidney (i.e. about 15 Gy for a cumulative radioactivity of 9 GBq). These predicted mean organ doses are thus below the limiting organ absorbed doses fixed to 1.5 Gy in BM and 23 Gy in kidney.

In the MSKCC study (Reidy 2017, NCT02609737), the tolerability after the first therapeutic cycle (mean cumulative radioactivity: 8.55 GBq; range: 6.94 - 9.43 GBq) was good with 17/19 subjects experiencing mild to moderate haematotoxicity and only 2/19 subjects experiencing reversible Grade 3 leukopenia. This treatment led to organ absorbed doses of 0.077 Gy/GBq in BM (i.e. about 0.7 Gy for a cumulative radioactivity of 9 GBq). The predicted BM absorbed dose is thus below the limiting organ absorbed dose fixed to 1.5 Gy.

The present study will include a different population with different sstr2 expression profile. However, the good tolerability in NET patients gives a reasonable safety margin. Moreover, the predicted organ absorbed doses are below the commonly defined thresholds (1.5 Gy in BM and 23 Gy in kidney) with a cumulative radioactivity of 9 GBq. From a safety point of view, all these factors taken together allow to start with a cumulative radioactivity of 9 GBq in this different population.

In both Wild 2014 and Reidy 2017 studies, consistent tumour absorbed doses were observed in NET subjects with median tumour absorbed doses of 7.0 and 7.2 Gy/GBq, respectively. Thus, in NET subjects administered with a cumulative radioactivity of 9 GBq, median tumour absorbed doses of 63 to 65 Gy that are in the range of ablative doses (Kalemkerian 2011) could be reached. Sstr2-positive non-NET tumours are known to express less sstr2 at tumoural cells surface but it is anticipated that significant tumour doses could be reached with the starting cumulative radioactivity of 9 GBq. Moreover, all subjects have the possibility to receive additional cycles of ^{177}Lu-OPS201 if they tolerate the treatment show clinical benefit and have

not exceeded the limiting organ absorbed doses. During additional cycles, the BM dose limit is increased to 2 Gy for subjects who did not experience Grade 3 or more haematotoxicity during the two first cycles. Indeed, 2 Gy is a generally accepted safety limit (Verburg 2013, Rolleman 2010, ICRP Publication 128) that allows more therapeutics options for those subjects who demonstrated good tolerance during the core trial. The choice of the activities and the possibility to administer additional cycles thus prevent underdosing subjects who may benefit from the treatment with ^{177}Lu-OPS201.

1.7.2.4 Maximum Cumulative Radioactivity of ^{177}Lu-OPS201

During radioactivity escalation, it is planned not to exceed the cumulative radioactivity of 12.9 GBq (7.4 GBq followed by 5.5 GBq). This value is indeed lower than the cumulative radioactivity of 15 GBq (two cycles of 7.5 GBq) that was not tolerated by NET subjects in Reidy 2017 study when given in two cycles of 7.5 GBq each (See Section 1.5.2). The statistical modelling performed based on this data showed that a dose-thrombocytopenia curve did predict a maximum tolerated cumulative activity (MTCA) around 13.7 GBq in subjects with NET. Moreover, to minimize the number of subjects who could be exposed to radioactivity exceeding the MTCA, a statistical Bayesian modelling approach will be implemented during the study to estimate a more precise radioactivity-DLT and organ radiation absorbed dose curve in order to guide further radioactivity selection and predict the radioactivity that could be tested in the next cohort of radioactivity escalation.

1.7.2.5 Peptide Mass Dose of ^{177}Lu-OPS201

As described in Section 1.4.5, the increase of peptide mass dose has been shown to improve tumour-to-background ratio and thus it is hypothesised that higher dose of peptide may improve the safety by reducing the radiation exposure in organs like BM or liver. Thus, a fixed peptide mass dose of 300 µg (±15%), that is higher than the dose of ≤100 µg used in both Wild 2014 and Reidy 2017 studies, has been chosen for the escalation cohorts. This choice is also substantiated by the work of Dalm (Dalm 2016a) showing that the optimal peptide dose in a mouse model of SCLC (H69) was 1 µg (equivalent to a dose of 250 µg in human).

In the phase I of this study, in addition to the 300 µg (±15%) peptide mass dose, safety and dosimetry with a higher peptide mass dose of 700 µg (±15%) will be evaluated. Therefore, once the first cycle of a radioactivity (e.g. 6 GBq followed by 3 GBq) has been shown to have acceptable tolerability with the lower peptide mass dose (300 µg (±15%)), the cohort will be repeated with the same radioactivity but with the higher peptide mass dose (700 µg (±15%)). The 700 µg peptide mass dose has been chosen since it allows the testing of a significant range of peptide mass doses and to clearly differentiate from the lower peptide mass dose. Moreover, this peptide mass dose is still well below the doses tested in the toxicology species (see calculations in Table 3).

Table 3 summarises the safety margins for each species used in toxicology studies based on the Human Equivalent Dose calculated from body surface area (Food and Drug Administration (FDA) Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers) (FDA Guidance).

Table 3 Toxicology Studies with ^{nat}Lu-OPS201 and OPS201: Estimated Safety Margin Study/Species based on Human Equivalent Dose based on Body Surface Area

Study	Dose	Estimated safety margin[a]
Study D-FR-01072-002	0.012 mg/kg of OPS201 (700 µg)	-
Single dose minipig Study I[redacted]	NOAEL = 1.56 mg/kg of ^{175}Lu-OPS201 in OPS201 (10:90 mol/mol) 1.40 mg/kg of OPS201	OPS201: 106
14-day repeated dose rat Study I[redacted]	NOAEL = 20 mg/kg/day of ^{175}Lu-OPS201 in OPS201 (10:90 mol/mol) 18 mg/kg of OPS201	OPS201: 242

NOAEL=no observed adverse events level
a based on Human Equivalent Dose based on body surface area (divided by 1.1 for minipig and 6.2 for rats)

For a 60-kg subject, a human dose of 700 µg of OPS201 (12.5 µg/kg) results in safety margin for OPS201 of about 106 times the human equivalent dose for minipigs and 242 times the human equivalent dose for rats.
The 2.3-fold increase in peptide mass dose between 300 and 700 µg (±15%) is justified since both doses are well below the doses tested in animals and since no pharmacological activity is expected.
A more detailed description of administration procedures is given in Section 6.1.

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 Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented.

FDA, 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials.

In addition, the 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.

1.9 Population to Be Studied

Tumours with significant sstr2 expression other than NET will constitute the target tumour types in the present study. In this phase I/II study, the subject population enrolled to receive ^{177}Lu-OPS201 will be limited first to pre-treated subjects with limited disease (LD)- or ED-SCLC and pretreated subjects with metastatic HR+/HER- BC (see full definition in Section 3.1), which are expressing sstr2 and displaying higher tracer uptake than non-tumoural liver parenchyma on ^{68}Ga-OPS202 PET/CT scans. Due to the late metastatic or advanced stage of the disease and progression or failure of response to standard-of-care (SoC) treatments, this population has in general a limited life expectancy. The line of therapy chosen for each cancer is the line for which the subject has exhausted validated treatments considered by the medical community and regulatory agencies as the SoC.

Note: Subjects with active known infection with human immunodeficiency virus (HIV) requiring systemic treatment or known acquired immunodeficiency syndrome (AIDS)-related illness, or known active hepatitis B or C infection that would pose a risk to subject safety or interfere with the study evaluation, procedures or completion will not be permitted screening for this study.

Preclinical and clinical observations indicate that the therapeutic effect of radiotherapy is partially immune mediated (Demaria 2004, Brody 2010; Golden 2015, Rodriguez-Ruiz 2016, Hiniker 2016, Tang 2017). Cell death induced by radiations is thought to be immunogenic and results in modulation of lymphocyte effector function in the tumour microenvironment promoting local control (Walle 2018). Several synergistic mechanisms exist that relate to radiation and the subsequent immune response. These include tumour antigen release and increased priming, tumour adjuvant release, the deletion of anergic and regulatory T cells, as well as T cell activation, antigen processing machinery, death receptor upregulation, induction of cytokines and chemokines and increased immune-cell trafficking. One synergistic interaction is the abscopal response, in which radiation acts as an in situ vaccine leading to increased control of distant disease sites. Another type of interaction is the immunogenic modulation, in which changes occur in the tumour microenvironment and any residual cancer cells leading to immune-mediated clearance of remaining local disease. Allowing inclusion of immunocompromised subjects in the study may render the interpretation of the study results difficult as would very likely interfer with these synergistic mechanisms.

Active hepatitis causes inflammation of the liver (Suhail 2014), and tissue injuries may impact the quality of normal liver imaging. The uptake in the non-tumoural liver tissue is used to estimate the tumour-to-background uptake ratio to assess both safety and efficacy of ^{177}Lu-OPS201 and the performance of ^{68}Ga-OPS202. In addition, changes in biological liver parameters may confound the assessment of safety parameters in terms of possible relationship to the investigational product. Hence, in the absence of a minimal product characterisation at this stage, it is reasonable that subjects with active hepatitis B or C be excluded from these studies.

1.9.1 Disease

Progress in the management of patients with SCLC has been modest in the past 20 years, the main contribution to improving patient survival has been provided by concurrent radiotherapy and management prophylactic cranial irradiation. Chemotherapy with etoposide and platinum remains the standard treatment whereas irinotecan and cisplatin has been demonstrated to be superior in selected populations. Although patients usually have an excellent response to chemotherapy with or without initial radiotherapy, nearly all will relapse with local or distant disease and eventually die. Tumour cells at progression are less sensitive to treatment with cytotoxics, therefore, treatment selection will depend on the time of relapse or progression. However, despite strides in the management of SCLC, there has been little change in survival over the past 2 decades for limited- or extensive-stage disease. Indeed, very few new agents with activity in SCLC have been identified (rovalpituzumab tesirine for high expressing DLL3, anti -PDL1), even as identification of molecular targets and targeted therapies has proceeded at a brisk pace in non-SCLC. Clinical and basic research continues to identify better treatment strategies that help increase the duration and effectiveness of treatment of patients with SCLC refractory or relapsing after chemotherapy regimens.

Patients with HR+ HER2- metastatic BC often respond to hormone therapy alone or in combination with targeted agents, which can reduce tumor burden and symptoms with generally fewer side effects and toxicities than chemotherapy. Furthermore, modern oestrogen therapy appears to prolong progression and possibly survival compared with older oestrogen treatments.

However, few if any patients with metastatic BC will be cured and the goal of therapy is, principally, palliation. All efforts are focusing on choosing the therapy that is most likely to stabilise or reduce the burden of disease with the fewest side effects and maintain that therapy until either unacceptable toxicity is evident or disease progression occurs.

Over the last decade, several prospective randomised clinical trials have demonstrated that addition of agents that operate in different ways than through hormone receptor interference can enhance the benefit seen with oestrogen therapy alone. In particular, cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with oestrogen therapy started to be used as a first-line therapy. Three separate agents, palbociclib, ribociclib and abemaciclib, which inhibit CDK 4/6, improve progression-free survival (PFS) when added to estrogen therapy as first-line or subsequent therapies. These trials have not yet demonstrated an overall survival (OS) benefit. However, the PFS benefit is considerable. Everolimus, an inhibitor of the mechanistic target of rapamycin (mTOR), has also demonstrated improved PFS when added to endocrine tharpy in the hormone-resistant setting. At this time, there are no randomised trials comparing the various CDK 4/6 inhibitors, everolimus, or their combination in patients receiving hormone therapy. However, there is a need in finding predictive biomarkers beyond the oestrogen receptor, determining whether to continue these agents beyond disease progression, creating novel combinations with other treatments or evaluating the sequence of treatment over different lines of metastatic disease.

For the limited percentage of patients who have extensive visceral metastases with evidence of end-organ dysfunction, treatment starts with first-line chemotherapy. This approach aims to maximise the chances of an early, meaningful, and more rapid response.

For patients with metastatic HER2-negative BC who have a germline *BRCA* mutation, the use of poly adenosine diphosphate ribose polymerase (PARP) inhibitors is discussed.

The optimal sequence of single endocrine agents and combinations with targeted agents is currently unknown and is a research priority. Data beyond progression to better understand the efficacy of each class of agent when given after the other is awaited. In this context, it is important to evaluate new treatment modalities to address refractory disease, relapsed disease or intolerance to treatment with the newly approved agents.

1.9.2 Sstr2 Expression in Cancer

The selection of the tumours of interest was performed by combining internal IHC data and literature review including IHC data but also in vivo uptake of radiolabeled somatostatin analogues, i.e. Octreoscan® or ^{68}Ga-DOTATATE/TOC:

- **Small cell lung cancer (SCLC):** Ipsen internal IHC data showed that 32.5% of the SCLC samples (tumour TMA) expressed sstr2. This proportion is even higher in the literature with 32 to 68% of positive SCLC samples (Papotti 2001, Righi 2010, Lapa 2016). Uptake of ^{68}Ga-DOTATOC/TATE was also reported in 67% (16/24) of the primary tumours in subjects with metastatic SCLC with a high uptake in 50% of the subjects (12/24). Metastatic sites were correctly identified by PET/CT with ^{68}Ga-DOTATOC/TATE in adrenals, lymph nodes and bone and in a lesser extent in brain and liver (Sollini 2013). In another study (Lapa 2016), 10/21 (48%) with ED-SCLC showed a significant uptake of ^{68}Ga-DOTATATE. Four subjects (19%) showed positive uptake (greater than the liver) in all lesions. And 6/21 (29%) were rated intermediate since most of the lesions showed positive uptake.
- **Hormone receptor positive HER2 negative breast cancer (HR+/HER2- BC):** two internal IHC studies showed positive sstr2 expression in the HR+ BC samples (24% of samples in a TMA study and 63% in sections). These results correlate with literature data

(Kumar 2005, Frati 2014). Moreover, several studies performed in small cohorts showed the feasibility of sstr-mediated nuclear imaging in BC subjects. In these studies, sensitivity for primary BC ranged from 36 to 100%. In a subset of the studies lymph nodes lesions were visualised, but sensitivity was lower compared to that for primary tumours. Most of these studies were performed with ^{111}In-DTPA-octreotide or ^{99}T-octreotide (Dalm 2016b).

Note: Male BC is a rare disease, representing 0.5% of all BCs (Nilsson 2011). Male BC shows some biological differences from female BC (Giordano 2004, Anderson 2004) and is contrasted in age at diagnosis, histological type, stage of disease, tumour grade, gene and ER expression (Shandiz 2015). Poorer survival outcomes were noted in male BC (Gnerlic 2011; Abreu 2016). Due to the very low frequency of male BC and major differences between male and female BCs, it is anticipated that in a study with limited sample size it is unlikely that a male subject with BC would be eligible and included in the study, and if any, the results generated may considerably increase data heterogeneity in the BC group. No IHC studies were performed in male BC samples, the sstr2 expression in HR+ HER2- male BC is thus not characterised.

To select the appropriate target population, tumours expressing sstr2 will be identified and documented through the lesion uptake of the companion diagnostic imaging product (^{68}Ga-OPS202) during the screening period. Only subjects showing at least two avid lesions of ≥20 mm on longest diameter with 1.5-fold or greater uptake than the non-tumour liver and lung tissue on PET/CT and with ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by the central reader will be enrolled for treatment with ^{177}Lu-OPS201.

Study population will thus be carefully selected to avoid administrating ^{177}Lu-OPS201 to subjects whose tumours may have non-adequate level of sstr2 expression and for whom consequently a potential benefit is not expected. Including only subjects with sufficient tumour radioactivity uptake (greater than non-tumoural liver parenchyma) and an appropriate matching of lesions on molecular imaging (^{68}Ga-OPS202 and ^{118}F-FDG-PET) also offers the advantage to avoid having too much radioactivity available to accumulate in off-target and sstr2 expressing organs like BM, pancreas or pituitary gland.

2 PURPOSES OF THE STUDY AND STUDY OBJECTIVES

2.1 Rationale and Purpose of the Study

Several types of tumours other than NET 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 yields an important promise in a personalised treatment approach such as theranostic combining imaging and therapy. The somatostatin analogue 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 Kd=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 beta minus emitting radionuclide, with a mean energy of 0.133 MeV and a mean penetration depth of 0.23 mm (Bodei 2013). In addition to beta-emission, ^{177}Lu has gamma rays which allow performing SPECT images and consequently dosimetry.

Non-NET tumours with significant sstr2 expression will constitute the target tumour types in this study. To identify the appropriate target population, an sstr2 molecular imaging radionuclide, ^{68}Ga-OPS202, will be used in conjunction with PET scanning during the screening period as a companion diagnostic imaging product and only subjects showing avid lesion uptake of ^{68}Ga-OPS202 in target tissue (primary tumour, lymph nodes and/or metastases) will be included in the study.

The antagonist therapeutic compound itself (^{177}Lu-OPS201) and related agonist compounds (^{177}Lu-DOTATATE) have already demonstrated anti-tumour activity in Grade 1 and 2 GEP-NET that are known to overexpress sstr2. Moreover, in a preclinical model (NCI-H69) with a level of sstr2 expression in the same range of some SCLC biopsy samples, ^{177}Lu-OPS201 presents a potential competitive advantage due to its specific binding properties as compared to ^{177}Lu-DOTATATE and demonstrated higher uptake and inhibition of tumour growth (Dalm 2016a) and confirmed with internal study. Regarding breast cancer, a preclinical study with a ER+/HER2- PdX model with heterogenous level of sstr2 expression demonstrated a 2-fold higher uptake on the tumour for ^{177}Lu-OPS201 versus ^{177}Lu-DOTATATE (Dalm 2017).

The compound ^{177}Lu-OPS201 and its companion diagnostic imaging product ^{68}Ga-OPS202 may offer a treatment option beyond standard of care for cancers such as LD- or ED-SCLC or metastatic HR+/HER2- BC (refer to eligibility criteria Section 4.1.1, criterion #3) where there are still high unmet clinical and therapeutic needs.

The purpose of the phase I of the study is to evaluate the safety and tolerability of the compound ^{177}Lu-OPS201 in this new population with a different benefit-risk ratio 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. The purpose of the phase II is to evaluate efficacy in selected sstr2-positive tumour types and further assess the safety of ^{177}Lu-OPS201.

Overall, the phase I/II study will evaluate a theranostic approach combining screening and assessment of subjects with the companion diagnostic imaging product (^{68}Ga-OPS202) and therapy with ^{177}Lu-OPS201.

2.2 Study Hypotheses

Phase I

^{177}Lu-OPS201 will be sufficiently safe to permit clinical investigation in phase II when administered in previously treated subjects with LD- or ED-SCLC and in previously treated metastatic HR+/HER2- BC, expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans.

Phase II

Previously treated subjects with LD- or ED-SCLC, or metastatic HR+/HER2- BC expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans and treated with ^{177}Lu-OPS201 will attain a clinically meaningful objective response rate (ORR), which is superior to the historical ORR obtained by current SoC treatment.

2.3 Study Objectives

2.3.1 Primary Objectives

Phase I

To evaluate the safety and tolerability and to define the MTCA of fractionated intravenous (i.v.) administration over two cycles of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans.

Phase II

To evaluate the ORR of fractionated i.v. administration of ^{177}Lu-OPS201 in previously treated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans.

2.3.2 Secondary Objectives

Phase I

- To determine the whole-body distribution and pharmacokinetics (PK) of ^{177}Lu-OPS201 after each administration.
- To determine the radiation dosimetry of ^{177}Lu-OPS201 (organ exposure to radiation) after each administration.
- To determine the PK of OPS201 in plasma and urine.
- To describe the preliminary anti-tumour activity of ^{177}Lu-OPS201.
- To evaluate PFS until Long-term Follow-up Visits up to 2 years after the End of Core Trial (EOCT) Visit.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 SPECT/CT.
- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT and tumour response to ^{177}Lu-OPS201.

Phase II

- To evaluate the efficacy of ^{177}Lu-OPS201 using Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 and/or Positron Emission Tomography Response Criteria In Solid (PERCIST) v1.0 criteria, volumetric CT and modified PERCIST using ^{68}Ga-OPS202 PET scans and modified RECIST using the ^{68}Ga-OPS202 avid lesions.
- To evaluate PFS until long-term follow-up visits up to 2 years after the EOCT Visit.
- To estimate the 1-year OS rate.
- To further evaluate the safety profile of ^{177}Lu-OPS201.

- To evaluate the association between uptake on ^{68}Ga-OPS202 PET/CT with tumour response to ^{177}Lu-OPS201 therapy.
- To determine the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and estimate its correlation with the uptake on ^{177}Lu-OPS201 SPECT/CT.
- To evaluate the impact of ^{177}Lu-OPS201 on the health-related quality of life of treated subjects.
- To estimate the proportion of sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by SUV in subjects screened for ^{177}Lu-OPS201 treatment.
- To further assess some PK and dosimetry parameters of ^{177}Lu-OPS201 based on the phase I results.

2.3.3 Exploratory Objectives

Phase I/II

- To explore renal and haematological safety by measuring urinary specific biomarkers and deoxyribonucleic acid-double strand breaks (DNA-DSB) and DNA repair in peripheral lymphocytes (at selected centres).
- To evaluate the tumour microenvironment, transcriptomics, DNA repair, gene mutation in tumour as compared to germinal mutation and other markers of interest through assessment of tumour biopsies.
- To collect biobank samples for future analysis of circulating markers (optional, additional informed consent required).
- To evaluate the association between the tumour uptake of ^{68}Ga-OPS202 and sstr2 expression on tumours as determined by IHC.
- To generate a model integrating PK, pharmacodynamics, dosimetry, anti-tumour activity and safety data if warranted by the data.

3 STUDY DESIGN

3.1 General Design and Study Schema

The proposed study is a phase I/II, multicentre, open-label study of ^{177}Lu-OPS201 therapy with companion diagnostic imaging product ^{68}Ga-OPS202 PET/CT in previously treated subjects with locally advanced or metastatic solid tumour expressing sstr2 who progressed under or after, failed to respond to, or are intolerant or having a contraindication to available SoC treatment options and are deemed suitable for treatment with ^{177}Lu-OPS201 as per the investigator's clinical assessment and/or their individual disease state. More specifically:

- Subjects who had ED-SCLC at presentation who have progressed on or after one line of standard chemotherapy. If a subject had LD-SCLC at presentation and received surgery and/or radiotherapy as first line treatment (with or without chemotherapy) and has localised relapse, further local treatment (such as surgery) should be considered in addition to the chemotherapy options.
  For subjects with either ED-SCLC or LD-SCLC, if subjects relapse more than 6 months after first-line treatment, re-treatment with their initial regimen is recommended. Subjects may have received prior immunotherapy.
- Subjects with HR+/HER2- metastatic BC after failure of prior SoC treatments and who have received, if indicated, at least one line of hormonal therapy, CDK4/6 inhibitor for advanced or metastatic disease and at least one line of chemotherapy for metastatic disease; subjects with *BRCA*-mutated metastatic disease who may have received a PARP inhibitor, if available, are eligible; prior adjuvant hormonal treatment and prior adjuvant chemotherapy are allowed.

Once the maximum tolerated cumulative radioactivity is reached and the appropriate peptide mass determined, additional subjects may be treated at this radioactivity/peptide dose, per tumour type cohort.

A clinical research Master Protocol in selected indications (basket design) will encompass this biomolecular target study protocol together with other study protocols targeting the same receptor (sstr2) and will describe the overall background, rationale, objectives, design, methodology and organisation of the overall sstr2-positive cancer research project for OPS201 and OPS202.

3.1.1 Study Sites

This study will be conducted at approximately 30 global clinical sites. Eight of these sites will participate in phase I and all sites in phase II. Participating regions are planned to be North America, Europe and Asia-Pacific. Additional sites may be added.

3.1.2 Number of Subjects

During phase I, up to 30 subjects will be enrolled for treatment with ^{177}Lu-OPS201. Based on the current knowledge on the proportion of subjects presenting with sstr2-positive tumours, it is anticipated that approximately 55 to 60 subjects will need to be administered ^{68}Ga-OPS202. Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with all the other inclusion/criteria met, the administration of ^{68}Ga-OPS202 and subsequent PET imaging will be stopped. Selection of sstr2-positive tumours for the treatment with ^{177}Lu-OPS201 will be revised in a protocol amendment.

During phase II, approximately 172 subjects (76 subjects with SCLC and 96 with BC) are planned to be enrolled for the Simon's optimal two-stage design. In this study phase, it is anticipated that approximately 340 subjects will need to be administered ^{68}Ga-OPS202 for PET

imaging screening. However, recruitment will be stopped once the number of required evaluable subjects (i.e. 76 subjects with SCLC and 96 with BC) is reached.

Further cohorts of subjects with other tumours expressing sstr2 could be added in this protocol according to the advances in the preclinical and clinical knowledge on ^{68}Ga-OPS202 and ^{177}Lu-OPS201 and emerging published data on the diseases. In this case, the additional number of subjects will be estimated based on standard of care historical response (e.g. ORR/best overall response (BOR)) of the corresponding disease.

3.1.3 Pre-treatment Period

A subject that qualifies will receive ^{68}Ga-OPS202 and will be imaged on PET/CT. Subjects with at least two sstr2 avid lesions of ≥20 mm in the longest diameter on ^{68}Ga-OPS202 PET/CT scan, confirmed by central read and having ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reader will then be treated with ^{177}Lu-OPS201.

Note: an application for a substantial amendment will be submitted for approval by the CAs and/or ECs (as applicable) before initiating changes to the study conduct.

3.1.4 Treatment Period - Phase I

Phase I is a multicentre, open-label, single-arm study designed to primarily investigate the safety and tolerability of ^{177}Lu-OPS201 following fractionated i.v. administrations in pretreated subjects with locally advanced or metastatic cancers expressing sstr2 as identified by ^{68}Ga-OPS202 PET/CT scans. This phase will encompass both radioactivity escalation and peptide mass dose evaluation.

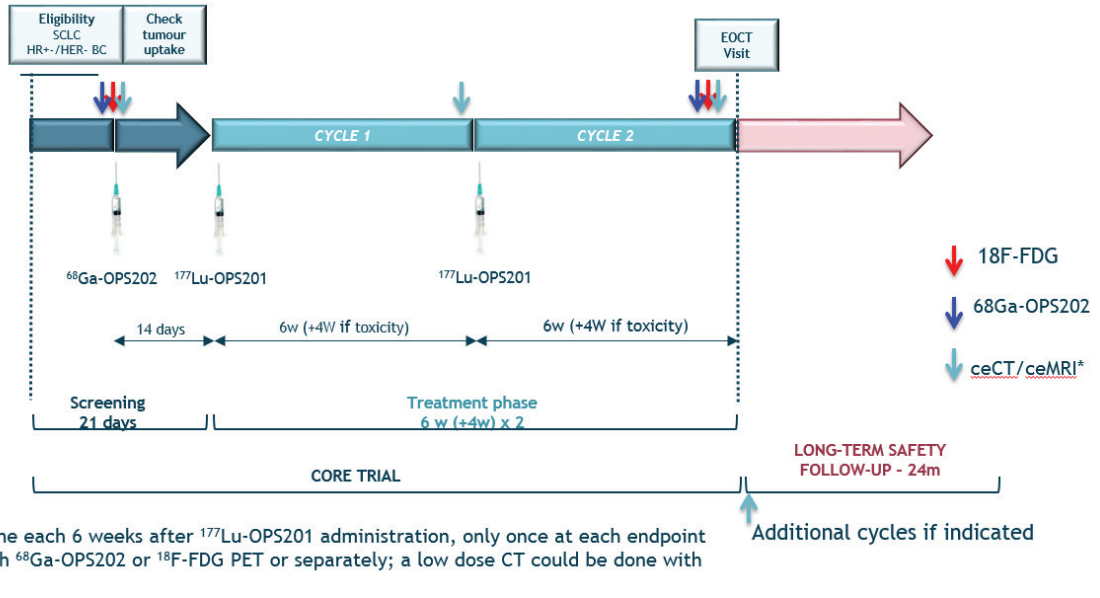
3.1.4.1 Radioactivity Escalation

The aim of the radioactivity escalation is to determine the MTCA and recommended phase II regimen.

In the core treatment period of phase I, up to three radioactivity levels of ^{177}Lu-OPS201 are planned to be tested with the radioactivity delivered in two administrations: one loading dose followed by a lower maintenance dose, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered) (see Figure 3).

The DLT assessment period is defined from the first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration. The DLT assessments will be performed over 6 weeks (up to 10 weeks in case of AEs that need to be adequately recovered) between first and second administration and 6 weeks between second administration and EOCT visit. During this period, subjects will have repeated imaging for the calculation of individual dosimetry data and will be monitored for signs of toxicity. Tumour response will be assessed based on ^{18}F-Fluorodeoxyglucose (FDG) PET at screening and 6 weeks after the second administration of ^{177}Lu-OPS201 and ceCT or contrast enhanced magnetic resonance imaging (ceMRI) scans at Screening and at 6 weeks after the first and second ^{177}Lu-OPS201 administration. Tumour response will also be assessed based on ^{68}Ga-OPS202 PET at screening and 6 weeks after the second administration of ^{177}Lu-OPS201. A long-term follow-up period will start after EOCT visit. Subjects will be followed-up every 3 months thereafter, until 24 months, death or withdrawal of full consent, whichever occurs first. In case the subject receives optional additional cycles (see Section 3.1.4.1.6) the 24-month follow-up period will start at the end of the last cycle of ^{177}Lu-OPS201.

Figure 3 Phase I Study Design Scheme (Without Additional Cycles)



3.1.4.1.1 Definition of the MTSA and MTCA

The purpose of the radioactivity escalation is to determine the MTCA. If not feasible, the maximum tolerated single activity (MTSA) or the maximum administered cumulative activity (MACA) will be determined as indicated below.

The MTCA is defined as the maximum cumulative radioactivity that may be administered following fractionated i.v. administrations of at least 6 weeks apart, so that:

- no more than 33% of the subjects experience a DLT after first or second administration of ^{177}Lu-OPS201 (see DLT definition in Section 3.8.1.1) and/or
- no more than 10% of the subjects have cumulative absorbed dose in each target organ exceeding the acceptability limits (1.5 Gy in BM and 23 Gy in kidney) after second administration of ^{177}Lu-OPS201.

The MTSA is defined as the highest single radioactivity that can be given so that no more than 33% of the subjects experience a DLT during Cycle 1. The MTSA will be determined in case of unacceptable toxicity seen after first administration of ^{177}Lu-OPS201.

The MACA will be determined if the MTCA is not reached during the dose escalation.

3.1.4.1.2 Cohorts Description

The planned radioactivity escalation will be conducted over three cohorts from a starting cumulative radioactivity of 9 GBq up to a maximum cumulative radioactivity of 12.9 GBq (see Figure 5).

The size of the cohorts will be three to five subjects. Once three subjects of the cohort complete Cycle 2 or discontinue early during Cycle 2, the cohort will be considered as complete. No more than five subjects should be enrolled per cohort.

3.1.4.1.3 Dose Escalation Mode

Cohorts will be enrolled using the following escalation approach:

- starting cumulative radioactivity of 9 GBq of ^{177}Lu-OPS201 fractionated into one administration of 6 GBq followed by a second administration of 3 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).

- maximum cumulative radioactivity of 12.9 GBq of ^{177}Lu-OPS201 fractionated into two administrations, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered).
- maximum radioactivity administrable in one cycle is 7.4 GBq of ^{177}Lu-OPS201.
- the inter-cohort radioactivity escalation will be performed by maximum increment of 2 GBq.

The predefined escalation scheme is described in Table 4. However, if DLTs are reported in Cohort 1 from the first administration of 6 GBq, it may be decided to deescalate the administered cumulative activity and start a cohort receiving a cumulative activity of 7.5 GBq fractionated into an administration of 4.5 GBq followed by an administration of 3 GBq. Then, if this cumulative activity is well tolerated, another cohort receiving a cumulative activity of 9 GBq fractionated into two administrations of 4.5 GBq may be started. During the escalation, in case DLTs are reported or if radiation absorbed dose is predicted to exceed the acceptability limits in at least one organ, the escalation scheme may be revised so that radioactivity not exceeding the MTCA/MTSA could be tested in the next cohort of radioactivity escalation. A statistical Bayesian modelling approach will be implemented to produce a more precise radioactivity-DLT curve and organ absorbed dose curve to guide the radioactivity selection (see details in Section 11 and Appendix 1) and predict the MTCA/MTSA.

Table 4 Cohorts and Radioactivity Escalation Plan

Planned radioactivity escalation	Cohort 1	Cohort 3	Cohort 5
Cumulative (GBq)	9	11	12.9
Schedule (GBq)	6 + 3	7 + 4	7.4 + 5.5

Abbreviation: GBq=Gigabecquerel

Once the radioactivity escalation has been completed, the MTCA level may be repeated in a last cohort (see Section 3.1.4.1.5 for stopping rule and MTCA definition).

3.1.4.1.4 Data Review Board

The DRB for radioactivity and peptide mass escalation, consisting of a team of "permanent" decision makers (the core team), including selected principal investigators and Ipsen personnel, will review the safety and dosimetry data and jointly decide with the sponsor whether to proceed with the enrolment of the next cohort. A DRB charter will be developed in a separate document to define attendees and roles and responsibilities, as well as the data reports to be reviewed by the DRB and the review timepoints.

3.1.4.1.4.1 Proceeding to the Second Administration

The investigator should follow the following rules before proceeding to the second administration:

- subjects with DLTs after first administration will be discontinued from ^{177}Lu-OPS201.
- subject will be eligible for second administration of ^{177}Lu-OPS201 only if:
  - subject's blood cell counts and renal function are in the range defined in the study inclusion criteria (#7), within the treatment cycle
  - subject's organ absorbed doses did not exceed 1.5 Gy in BM and 23 Gy in kidney.

The radioactivity dose of the second administration will be adjusted based on dosimetry results to prevent exceeding limiting organ absorbed doses limits (1.5 Gy for bone marrow; 23 Gy for kidney). The planned maintenance dose for Cycle 2 may be revised in any eligible subject, if

the cumulative radioactivity is anticipated to exceed the predicted MTCA. In that case the maintenance dose will not exceed the predicted MTCA minus the loading dose. In any case, the maintenance dose will be adjusted in a way not to exceed the limiting organ absorbed doses.

3.1.4.1.4.2 Proceeding to the Next Cohort

The DRB meeting for radioactivity escalation will take place after three subjects of the radioactivity escalation cohort have completed two cycles of ^{177}Lu-OPS201. The DRB will review all available safety and dosimetry data from the study to decide if the escalation can proceed as planned (see Table 4).

If DLTs are reported, a statistical Bayesian modelling approach will be implemented to produce more precise radioactivity-DLT and organ absorbed doses curves to guide the radioactivity selection and predict a radioactivity not exceeding the predicted MTCA/MTSA that could be tested in the next cohort of radioactivity escalation.

If the starting cumulative radioactivity of 9 GBq is not well tolerated, another cohort with a decreased cumulative radioactivity will start. In this case, the cumulative radioactivity could be determined using the statistical Bayesian approach, for example, 7.5 GBq (one administration of 4.5 GBq followed by an administration of 3 GBq, 6 weeks apart (+ up to additional 4 weeks in case of AEs that need to be adequately recovered)).

3.1.4.1.5 Stopping Rules for Dose Escalation

The radioactivity escalation will be stopped as soon as:

- the MTCA and/or MTSA have been defined with good precision; or
- the maximum planned radioactivity of 12.9 GBq, fractionated into two administrations separated by 6 weeks, is administered without safety concerns and is thus defined as the MACA.

Once the radioactivity escalation has been completed, the MTCA level may be repeated based on the results of the Bayesian model in a last cohort of three to five subjects with the same peptide mass dose to confirm the safety profile. If the MTCA is not reached and if limiting organ absorbed doses are not exceeded at the highest planned radioactivity (12.9 GBq) and if no individual withdrawal criteria are met, the inclusion of an additional cohort with a higher cumulative radioactivity will be evaluated.

Note: an application for a substantial amendment will be submitted for approval by the CAs and/or ECs (as applicable) before initiating changes to the study conduct.

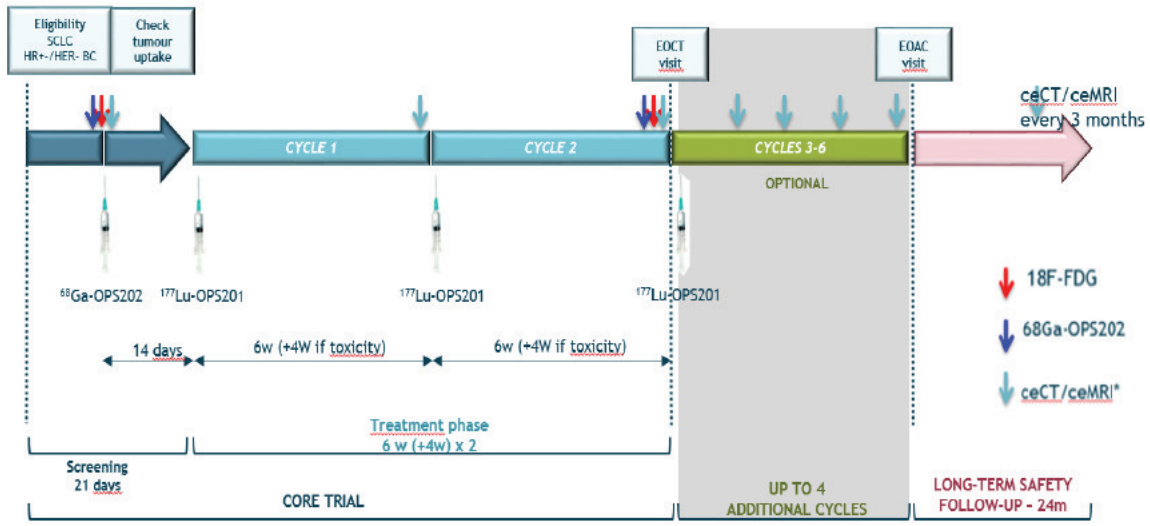
3.1.4.1.6 Optional Additional Cycles

If a subject tolerates well the treatment and shows clinical benefit (e.g. complete response (CR), partial response (PR), or stable disease) after the two first cycles, up to four additional cycles (^{177}Lu-OPS201 administration, 6 weeks apart) at a radioactivity adjusted based on dosimetry results can be administered to this subject provided limiting organ absorbed doses have not been exceeded (see Figure 4). The decision to administer additional cycles or any other anti-tumoural treatment is left 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:

- subject will be eligible for an additional administration of ^{177}Lu-OPS201 only if:
  - blood cell counts and renal function are in the range defined in the study inclusion criteria (#7), within the treatment cycle
  - organ absorbed doses did not exceed 1.5 or 2 Gy in BM (see details below) and 23 Gy in kidney.

The planned maintenance dose for any cycle will be adjusted such that the limiting organ absorbed doses (23 Gy in kidney, 2 Gy in bone marrow, if no Grade 3 or more haematotoxicity have been observed in this subject, otherwise limit in bone marrow is set to 1.5 Gy) is not exceeded.
Subjects who experience a significant toxicity (such as Grade 3 or 4 haematological toxicity or any DLT) will be allowed to continue to receive study treatment at a lower activity level at the discretion of the investigator and will be closely monitored for safety.
For these subjects, the End of Additional Cycles (EOAC) visit, with the same assessments as for an EOCT visit, will be performed 6 weeks after last ^{177}Lu-OPS201 administration. A 24-month long-term follow-up period will start after EOAC visit. Subjects will be followed-up every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first.

Figure 4 Phase I Study Design Scheme (With Additional Cycles)



* ceCT done each 6 weeks after ^{177}Lu-OPS201 administration, only once at each endpoint either with ^{68}Ga-OPS202 or ^{18}F-FDG PET or separately; a low dose CT could be done with each PET

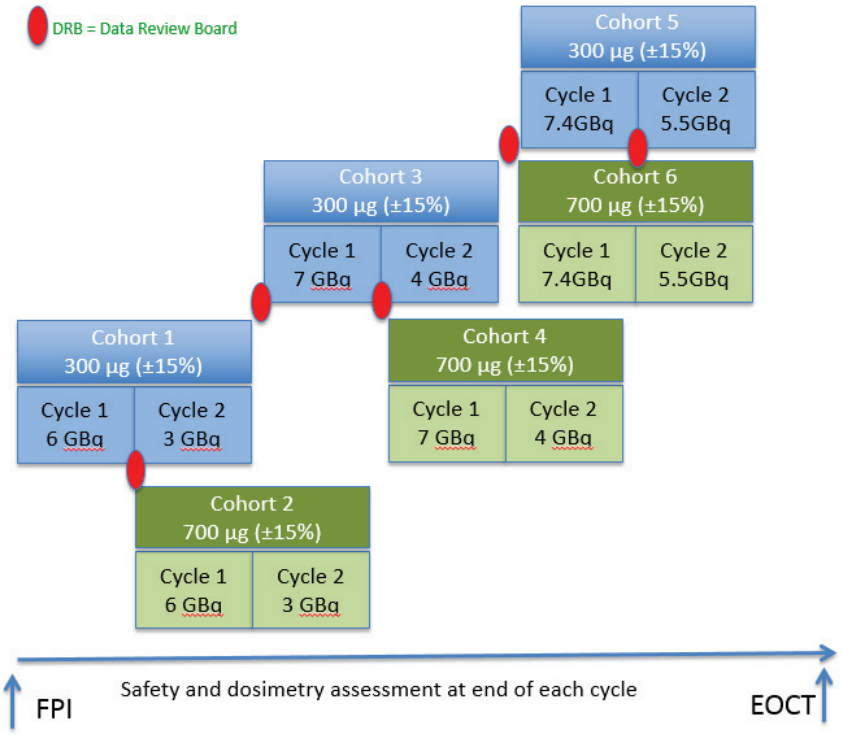
3.1.4.2 Peptide Mass Dose Evaluation

In parallel with the radioactivity escalation phase, once the first cycle of a radioactivity level is considered acceptably tolerated by the DRB, the radioactivity level will be repeated with a higher peptide mass dose (700 µg (±15%)). Three additional cohorts of three to five subjects will thus be enrolled in the peptide mass dose evaluation (see Figure 5). The schedule of assessments and safety evaluation in these cohorts will be the same as in the radioactivity escalation cohorts.
The DRB for peptide mass dose escalation will meet after the third subject of each cohort has received the first cycle of ^{177}Lu-OPS201 with DLT assessments performed. The DRB will review all safety and dosimetry data and allow the peptide mass dose escalation. The cohort with the high peptide mass dose (700 µg) will thus only start when the first cycle of the corresponding radioactivity level tested with 300 µg peptide mass dose has been evaluated by the DRB and has been considered acceptably tolerated.

Moreover, the administration of the second cycle of the peptide mass dose evaluation cohorts can only proceed once the second cycle of the corresponding radioactivity level has been considered acceptably tolerated (except for Cohort 6, where the radioactivity for the first cycle (7.4 GBq) is slightly different from the previous cohort (7.0 GBq), so Cohort 6 will start in

parallel of Cohort 5 (see Figure 5)). The same subject cannot participate in the radioactivity escalation cohort and the peptide mass dose cohort.

Figure 5 Initial Phase I Study Design Including Activity Escalation (in Blue) and Peptide Mass Dose Evaluation (in Green)



3.1.5 Treatment Period - Phase II

Phase II is a multicentre study with open-label multiple single arm cohorts using Simon's optimal two-stage design to evaluate the efficacy, as assessed by ORR, of treatment with ^{177}Lu-OPS201 in subjects with locally advanced or metastatic SCLC, or metastatic HR+/HER2- BC expressing sstr2, as identified by ^{68}Ga-OPS202 PET/CT scans.

Approximately 76 subjects with locally advanced or metastatic SCLC and approximately 96 subjects with metastatic HR+/HER2- BC deemed sstr2-positive on ^{68}Ga-OPS202 PET/CT scans will receive the ^{177}Lu-OPS201 treatment regimen recommended based on the results of the phase I. It is expected that two cycles of ^{177}Lu-OPS201 will be administered in subjects enrolled in phase II. Up to four additional cycles might be administered in subjects who tolerate the treatment well and show clinical benefit (CR, PR, or stable disease) after the first two cycles. These additional cycles will be administered at radioactivity adjusted based on dosimetry results, provided limiting organ radiation dose levels have not been exceeded.

Additional cohorts could be added to the study according to evidence based on preclinical and clinical work and data on ^{68}Ga-OPS202 and ^{177}Lu-OPS201, sstr2 expression and candidate diseases.

An independent safety assessment committee (ISAC) structured to assess safety in addition to efficacy will be established during phase II in order to make recommendations regarding protocol modifications to reduce risks to subjects enrolled in the trial.

Post-treatment Period

Subjects in each phase of the study will have 2-year follow-up after the end of the last ^{177}Lu-OPS201 Cycle, with a visit every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first.

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Endpoints and Evaluations

3.2.1.1 Phase I

The primary endpoint is the MTCA or the MACA if the MTCA is not identified during the phase I. The primary variables determining the MTCA will be the incidence of DLTs and the cumulative organ absorbed doses (Gy) during two cycles of treatment. The DLT assessment period for the determination of the primary endpoint starts from the first administration of ^{177}Lu-OPS201 and ends 6 weeks after the second administration.

3.2.1.2 Phase II

The primary endpoint is ORR over the two treatment cycles of the core study measured by the ICL. Objective response is defined as the sum of PR and CR measured by CT or MRI using RECIST version 1.1. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator. All images will be sent to an ICL for evaluation and confirmation of response (see Section 7).

3.2.2 Secondary Endpoints and Evaluations

3.2.2.1 Phase I

Pharmacokinetics, Biodistribution and Dosimetry

For PK, biodistribution and dosimetry of ^{177}Lu-OPS201, the endpoints are:

- Maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), maximal uptake (%), area under the curve (AUC) at the target lesions, discernible organs and blood and elimination half-life ($t_{½}$) of radioactivity concentrations in blood.
- Highest absorbed dose, Specific absorbed dose to the target lesions (Gy/GBq), Specific absorbed dose per organ (Gy/GBq) and Cumulative absorbed organ doses (Gy).

For PK of OPS201, the endpoints are:

- Pharmacokinetic parameters including, but not limited to, C_{max}, AUC, $t_{1/2}$, total plasma clearance (CL), apparent volume of distribution (V_d), cumulative amount (of unchanged drug) excreted into the urine (A_e), renal clearance, as measured in plasma and urine at defined timepoints.

Pharmacodynamic/Efficacy

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration compared to Screening as assessed by CT or MRI:
  - RECIST version 1.1 (tumour size is defined as the sum of the diameters of the target lesion in subjects who received ^{177}Lu-OPS201)
  - volumetric CT
- PFS as determined from start of study treatment until occurrence of tumour progression or death.

- BOR defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause.
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
- Changes in tumour uptake (assessed based on SUV_{max} and SUV_{mean}) on ^{68}Ga-OPS202 PET/CT from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle) as compared to clinical response and BOR.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to standard-of-truth (SOT) of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to SOT of ^{177}Lu-OPS201 SPECT/CT.

3.2.2.2 Phase II

Efficacy

All the below endpoints will be calculated per cohorts. All imaging endpoints will be assessed by blinded independent readers managed by the ICL.

- Durable response rate (DRR: CR or PR lasting ≥6 months)
- PFS as determined from start of study treatment until occurrence of tumour progression or death.
- Other response endpoints (same timepoints as for PFS):
  - disease control rate (DCR)
  - time to progression (TTP)
  - time to response (TTR)
  - duration of response (DoR)
- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration (each cycle) compared to baseline, as assessed by volumetric CT/MRI.
- OS at 1-year and 2-year follow-up as determined from start of study treatment until occurrence of death of any cause.
- Quantitative changes (SUV normalised by lean body mass $(SUL)_{max}$ and SUL_{mean}) in tumour-to-background ^{18}F-FDG-PET uptake using PERCIST version 1.0, from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).

- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle).
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
- Change in ^{68}Ga-OPS202 uptake on PET scan after the second ^{177}Lu-OPS201 administration (second cycle) as assessed by SUV_{max} and SUV_{mean} in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR.
- Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by the identification of avid lesions in subjects screened for ^{177}Lu-OPS201 treatment at baseline.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging using mGa-RECIST by subject-based analysis.
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by subject-based, organ-based and lesion-based analysis compared to SOT of ceCT (or ceMRI).
- Diagnostic sensitivity of ^{68}Ga-OPS202 imaging by both organ-based and lesion-based analysis compared to SOT of ^{177}Lu-OPS201 SPECT/CT.

Subject Reported Outcomes

- Changes in health-related quality of life scores from baseline to EOCT measured by EuroQoL 5-dimension 5-level (EQ-5D-5L) and The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).

Safety Endpoints and Evaluations

- Safety and tolerability measured by the type, nature, severity, expectedness and frequency of AEs overall and per grade according to the current version of the National Cancer Institute Common Terminology Criteria Adverse Event (NCI-CTCAE) (version 5.0) and significant laboratory abnormalities.

Pharmacokinetics, biodistribution and dosimetry endpoints and measurement timepoints for phase II will be defined according to the phase I results.

3.3 Exploratory Endpoints (Phase I/II)

3.3.1 Biomarkers

- Association between the uptake on ^{68}Ga-OPS202 PET/CT with sstr2 expression on tumours as determined by IHC.
- Change in renal safety biomarkers compared to baseline.
- Change from baseline in tumour microenvironment, transcriptomics, DNA repair, gene mutations and other disease markers of interest.
- Change from baseline in DNA repair capacity in blood.

3.3.2 Biobanking

The exploratory endpoint comprises biobanking of samples for future analysis, among subjects who consent. Analysis of additional biomarkers from the biobank samples will be performed outside the scope of the main study and reported separately.

Serum, cfDNA and whole blood ribonucleic acid (RNA) samples will be collected on Day 1 (or Day -1) of Cycle 1 before infusion and at Day 1 of Cycle 2 before infusion and at EOCT/EOAC/early withdrawal (EW).

3.4 Randomisation and Blinding

This is a nonrandomised, open-label study.

Independent readers will evaluate ^{68}Ga-OPS202 PET/CT and ^{18}F-FDG-PET/CT images 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 exam findings.

Independent readers are specialised radiologists and/or nuclear medicine physicians who are experienced in reading PET/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 (IRC).

3.5 Maintenance of Randomisation and Blinding

This is a nonrandomised, open-label study.

3.6 Study Treatments and Dosage

3.6.1 Investigational Imaging Product (IIP): ^{68}Ga-OPS202

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

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

The radiolabelling kit will be packaged and delivered to the investigational sites. A sufficient quantity of radiolabelling kit will be supplied as well as an acknowledgement of receipt form. The investigator's representative will receive:

- A Certificate of Compliance/Analysis for each batch of kit for radiolabelling that will be used during the study which reflect the product release statement.
- Material Data Safety Sheet.
- Packaging order.

The radiolabelling kit and all vials will be labelled. After preparation, the IIP will be placed in a shielding container and the container labelled. Each label will be designed in accordance with Appendix 13 of the European Union Good Manufacturing Practices (EU-GMP) and in accordance with specific local requirements if any.

Radiolabelling yields the IIP ^{68}Ga-OPS202 as a solution for injection. After quality control (QC) sampling, the volume to be injected into the subject is withdrawn from the IIP vial, containing up to 45 µg OPS202. This volume is determined to obtain the target radioactivity at the time of administration, taking into account the decay of ^{68}Ga. All subjects will receive at Screening visit a single dose of ^{68}Ga-OPS202 (IIP), with ^{68}Ga radioactivity of 150-200 MBq, injected intravenously. A single dose of ^{68}Ga-OPS202 will also be administered after two cycles at EOCT.

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

A more detailed description of preparation and administration procedures is given in Section 6.2.1.

3.6.2 Investigational Radio-Pharmaceutical Product (IRPP): ^{177}Lu-OPS201

The IRPP is manufactured and supplied directly to the clinical site from a central contract manufacturing organisation. It is manufactured by Sofie Co. dba Sofie (110 Clyde road, Somerset, NJ 08873, USA). The IRPP will be supplied in a type 1 borosilicate glass vial sealed with a chlorobutyl stopper and aluminium seal with a flip off cap, within a secondary shielding container and is shipped inside a temperature-controlled and Type A package for transporting radioactive materials.

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 EU-GMP and in accordance with specific local requirements if any.

The IRPP is a 20-mL solution for injection with OPS201 dose of either 300 µg (±15%) or 700 µg (±15%) and radioactivity of 3 to 7.4 GBq ^{177}Lu-OPS201. All subjects will receive a loading dose ranging from 4.5 to 7.4 GBq (±10%) and a maintenance dose ranging from 3 to 5.5 GBq (±10%), injected intravenously.

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

For renal protection purpose, an amino acid solution (Lysine and Arginine based) must be administered intravenously.

A more detailed description of administration procedures is given in Section 6.2.2.

3.7 Study Duration

In phase I, for subjects receiving only two treatment cycles of ^{177}Lu-OPS201, this study will consist of up to 3-week screening period and a 12-week dosing period (+ up to additional 4 weeks in case of AEs that need to be adequately recovered). A treatment cycle is defined as the timeframe of 6 (up to 10) weeks between two administrations or the timeframe of 6 weeks following the last administration. In case of logistical issues, the cycle could be extended by up to additional 2 weeks. Dosing period can be extended up to 36 weeks in case subjects receive up to four additional cycles (see Section 3.1.4.1.6). Subjects are thus expected to participate in this study for a minimum of 15 weeks and up to 39 weeks (+ up to additional 4 weeks in case of AEs that need to be adequately recovered). In all cases, a long-term follow-up lasting 24 months will start after the end of the last ^{177}Lu-OPS201 cycle.

For phase II, it is anticipated that the duration of the study will be identical to the duration in phase I; however, pending the results of phase I on recommended treatment regimen (doses and intervals) the study duration will be refined.

The subject's participation in the treatment period of the study will be considered to have ended at the EOCT or EOAC visit. The subject's participation in the 24-month follow-up period of the study will be considered to have ended when the subject dies, withdraws consent to the follow-up period, or ends the 24-month follow-up, whichever occurs first.

The overall duration of the study will be approximately 5.5 years. The study will be considered to have started when the first site has been initiated.

The study will be considered to have ended after the last subject has completed the last follow-up visit in the study.

3.8 Stopping Rules and Discontinuation Criteria

3.8.1 Individual Discontinuation Rules

A subject (or a legal representative) has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator at the institution.

The investigator and/or sponsor can decide to withdraw a subject from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the following reasons:

- Subject no longer experiences clinical benefit as determined by the investigator. If study treatment is withdrawn for this reason, the date this decision is to be recorded and every effort should be made to continue safety evaluations, tumour assessments, and collection of subsequent anticancer treatment information and follow-up information for survival.
- Unacceptable side effects the investigator feels may be due to study treatment.
- The investigator feels it is not in the best interest of the subject to continue on study.
- Subject participation in another clinical study using an investigational agent or investigational medical device.
- Necessity for treatment with other systemic anticancer therapy (non-protocol defined).
- Necessity for withholding study drug for greater than 6 weeks for study-treatment related AEs.
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilised) to use medically accepted methods of contraception.
- Female subjects who become pregnant.
- Request by the sponsor.
- Subject request to discontinue study treatment (with or without concurrent withdrawal of informed consent).
- Significant noncompliance with the protocol schedule in the opinion of the investigator or the sponsor (see protocol violation or deviation as defined in Section 13.1.2).

In addition, if any of the following occur, no further treatment will be administered:

- Cumulative kidney absorbed dose exceeds 23 Gy.
- Cumulative BM absorbed dose exceeds 1.5 Gy during core trial or up to 2 Gy during additional cycles, as determined by dosimetry of peripheral blood samples and imaging.
- Subject has not sufficiently recovered from an adverse event despite extension of the dosing interval by 4 weeks (such as delayed grade 3-4 haematotoxicity)
- Hypersensitivity to the active substance or to any of the excipients of the study drugs
- Radiological disease progression

Subjects who experience a significant toxicity (such as DLT or Grade 3 or 4 haematological toxicity) will be allowed to continue to receive study treatment at a lower activity level at the discretion of the investigator and will be closely monitored for safety.

Temporary discontinuation of treatment with ^{177}Lu-OPS201 could be decided upon occurrence of an intercurrent disease, which according to the investigator could increase the risks associated to the IRPP administration; major surgery, specific adverse reactions to ^{177}Lu-OPS201 that need time for resolution or stabilisation.

No radiation dose limits have been set for other organs than kidney and bone marrow either since the expected cumulative absorbed dose in these organs is well below the limits described in the ICRP guideline (e.g. liver) (ICRP Publication 41) or since no radiation dose limit is reported in the aforementioned guideline for this organ (e.g. spleen).

All cases of discontinuation will be discussed between the investigator and the sponsor.
A subject can also withdraw their consent to the treatment period but agree to take part in 24-month follow-up period. This will be captured in the medical file and in the electronic case report form (eCRF).

3.8.1.1 Definition of Dose Limiting Toxicity (Dose Escalation)

The DLTs are defined for any of the following IRPP-related AEs according to NCI-CTCAE scale version 5.0 that occur during the defined DLT assessment period (from the first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration):

- Grade 4 neutropenia lasting for seven or more consecutive days.
- Grade 3 and 4 febrile neutropenia.
- Grade 4 thrombocytopenia for seven or more consecutive days.
- Grade 3 thrombocytopenia complicated by a bleeding event.
- Grade 4 anaemia.
- Grade 3 anaemia requiring transfusion.
- Grade 3 or higher laboratory abnormalities of aspartate amino transferase/alanine amino transferase (AST/ALT) and/or bilirubin, with the following exceptions:
  - for subjects with Grade 1 AST/ALT at baseline (>upper limit of normal (ULN) to 3xULN), a AST/ALT level of >7.5xULN will be considered a DLT.
  - for subjects with Grade 2 AST/ALT at baseline (>3xULN to 5xULN), a AST/ALT level > 10xULN will be considered a DLT.
- any Grade 3 or higher acute kidney injury (creatinine >3x baseline or >4.0 mg/dL).
- Grade 3 or higher non-haematological toxicity excluding:
  - Grade 3 nausea, vomiting or diarrhoea for less than 72 hours with adequate supportive care
  - Grade 3 fatigue lasting less than a week
  - Grade 3 or higher electrolyte abnormality that lasts for less than 72 hours, is not clinically complicated and resolves spontaneously or with conventional medical interventions
  - Grade 3 or higher amylase or lipase not associated with symptoms or clinical manifestations of pancreatitis
- any toxicity related to ^{177}Lu-OPS201 resulting in a treatment delay of more than 4 weeks due to delayed recovery to baseline or resolution of any AE of Grade 2 or more (exception of alopecia and lymphopenia).
- Grade 5 toxicity (death)

DLT Assessment: During the DLT assessment period (from first administration of ^{177}Lu-OPS201 to 6 weeks after the second administration), two assessments over 6 weeks each will be performed. The first, between first and second administration and the second, between second administration and EOCT visit.

DLT Population: Subject will be evaluable for DLT if received Cycle 1 and Cycle 2 administrations and completed DLT assessment period (i.e. 6 weeks after second

administration) or stopped treatment because of a DLT during DLT assessment period.
If a subject is considered Not Evaluable for DLT due to withdrawal during DLT assessment period, he/she will be replaced by another subject.

3.8.1.2 Procedures for Subject Discontinuation

If a subject drops out or is discontinued from the treatment period of the study after IRPP administration and before planned study completion, an EW visit will take place within 6 weeks after the last IRPP administration. This visit will correspond to an EOCT visit (or EOAC visit if the subject dropout during additional cycles). Thereafter, follow-up visits will take place every 3 months. Subjects who discontinue study treatment for reasons other than disease progression (e.g. toxicity) should continue to undergo scheduled tumour assessments until the subject dies, experiences disease progression, withdraws consent to the follow-up period, or until the end of the two-year follow-up, whichever occurs first.

The reason for and date of withdrawal from the study must be recorded in the eCRF.

If the discontinuation is based on subject decision, every attempt will be made to determine the reason for discontinuation. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

Subjects withdrawn from the study for unacceptable AE(s) will be followed by the investigator until resolution or stabilisation of the AEs.

3.8.1.3 Replacement Rules

In phase I, a cohort will be considered as completed once three subjects of the cohort complete Cycle 2 or discontinue early during Cycle 2. If subjects discontinue for any reason other than a DLT (e.g. disease progression) before end of Cycle 2, they might be replaced.

3.8.2 Discontinuation of a Cohort or a Site or Study Termination

The phase I will be terminated once the MTCA has been determined. The phase II is designed with early stopping criteria, allowing any cohort to be closed early in case of futility.
A specific site or a given cohort can also be discontinued or the entire study may be terminated at any time if the sponsor judges it necessary for any reason. In that case, all scheduled procedures and assessments for subjects who are still in the study will be performed. Some possible reasons for the closure of a study site may include:

- failure of the investigator staff to comply with the protocol or with the GCP guidelines.
- safety concerns.
- inadequate subject recruitment.

Both safety and anti-tumour activity of ^{177}Lu-OPS201 in subjects in phase II as well as of subjects from phase I receiving additional cycles of ^{177}Lu-OPS201 will continue to be monitored by the DRB and by the ISAC on an ongoing basis. The decision to halt enrolment or to discontinue a subject or a cohort may be made by DRB and ISAC at any point if a safety signal or unacceptable toxicity are observed.
In case of premature discontinuation of a site or the complete study, depending on the reason(s) for the discontinuation, the sponsor will notify the investigator(s) affected in writing as to whether the ongoing subjects should continue the remaining IRPP dose administration(s).

3.8.3 Study Stopping Rules

Should, at the start of the study, 20 consecutive subjects fail screening due to ^{68}Ga-OPS202 PET/CT negative for sstr2 with all the other inclusion/criteria met, the administration of

^{68}Ga-OPS202 and subsequent PET imaging will be stopped. Selection of sstr2-positive tumours for the treatment with ^{177}Lu-OPS201 will be revised in a protocol amendment.

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 (with subject status), IIP/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).

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

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Eligibility Criteria for ^{68}Ga-OPS202 Imaging

4.1.1 Inclusion Criteria

All subjects must fulfil all the following criteria to undergo the ^{68}Ga-OPS202 imaging (phase I/II):

(1) signed informed consent prior to initiation of any study-specific activities/procedures.

(2) male (except for BC cohort) or female subject aged 18 years or older.

(3a) histologically confirmed cancer, that is locally advanced or metastatic disease, which has progressed during or after, failed to respond to, or for which there is poor tolerability or a contraindication to available SoC treatment options as per the assessment of the investigator; initially, subjects with the disease below may be considered:

(a) Subjects who had ED-SCLC at presentation who have progressed on or after one line of standard chemotherapy. If a subject had LD-SCLC at presentation and received surgery and/or radiotherapy as first line treatment (with or without chemotherapy) and has localised relapse, further local treatment (such as surgery) should be considered in addition to the chemotherapy options.
For subjects with either ED-SCLC or LD-SCLC, if subjects relapse more than 6 months after first-line treatment, re-treatment with their initial regimen is recommended. Subjects may have received prior immunotherapy.

(b) Subjects with HR+/HER2- metastatic BC after failure of prior SoC treatments and who have received, if indicated, at least one line of hormonal therapy, CDK4/6 inhibitor and/or everolimus for advanced or metastatic disease and at least one line of chemotherapy for metastatic disease; subjects with BRCA-mutated metastatic disease who may have received a PARP inhibitor, if available, are eligible; prior adjuvant hormonal treatment and prior adjuvant chemotherapy are allowed.

(4) disease must be unsuitable for curative surgical resection and must not be amenable to curative radiotherapy.

(5a) documented progressive disease (radiological, based on RECIST v1.1) within 3 months prior to first study drug administration. Screening study-related images should be sent to the ICL.
Note: All images of the two datasets documenting progression should be sent to ICL.

(6) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

(7a) adequate organ function determined within 28 days prior to ^{177}Lu-OPS201 administration, defined as follows:

- Haematological:
  - white blood cells (WBC) ≥3000/µL, with absolute neutrophil count ≥1000/µL, platelet ≥100,000/µL and haemoglobin ≥9 g/dL (without need for hematopoietic growth factor or transfusion support).
- Renal:
  - eGFR ≥55 mL/minute/1.73m^2
- Hepatic:
  - total serum bilirubin ≤2×ULN
  - -aspartate aminotransferase/ alanine aminotransferase ≤2.5×ULN (≤5×ULN if subject has liver metastases).

(8a) has a formalin fixed paraffin embedded tumour sample (archival tumour sample obtained within 1 month prior to consent) from the primary or metastatic lesion OR is willing to undergo newly obtained biopsy prior to first dose of study treatment. Subjects who are unable or do not consent to provide acceptable tissue may not be enrolled unless there has been prior agreement with the sponsor.
Note: the subject will be enrolled (if he/she fulfills all inclusion criteria and has no exclusion criterion) irrespective of the biopsy result

(9) estimated life expectancy >3 months.

Eligibility Criteria for Therapy (Phase I/II)

To receive ^{177}Lu-OPS201 therapy, each subject must fulfil all the eligibility criteria including the below criteria:

(10a) ^{68}Ga-OPS202 uptake in target tissue (primary tumour, lymph nodes and/or metastases) showing at least two avid (uptake ≥1.5 non-tumour liver and lung uptake) lesions of ≥20 mm in the longest diameter on PET/CT as confirmed by central reader.

(11) Radiologically, ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reader

The inclusion criteria for phase II will be refined based on the results from phase I as well as type of possible additional tumours and indications to be investigated and will be documented as part of a protocol amendment.

4.1.2 Exclusion Criteria

Eligible subjects must not have any of the following conditions (phase I/II):

(1) male subjects with BC.

(2a) unstable central nervous system metastasis defined as (any of the following):

- (a) Radiographic evidence of new or progressive brain metastases after prior radiation therapy with at least one brain metastasis measuring ≥1 cm in longest diameter on gadolinium-enhanced magnetic resonance imaging (MRI), and/or
- (b) Imaging following prior radiation is not consistent with pseudo-progression in the judgment of treating clinician, and/or
- (c) Evidence of diffuse leptomeningeal disease on brain MRI or by previously documented cerebrospinal fluid cytology.
  NOTE: discrete dural metastases are permitted.

Subjects with previously treated brain metastases (with no lesion measuring ≥1 cm in longest diameter on gadolinium-enhanced MRI at the time of evaluation for the study) may participate provided they are neurologically stable as defined by (all the following need to be met):

i. no evidence of progression by imaging and any neurologic symptoms have returned to baseline
ii. no use of steroids and anti-convulsants for at least 7 days prior to IRPP administration.
iii. no clinically significant mass effect, haemorrhage, midline shift, or impending herniation on baseline brain imaging.
iv. no significant focal neurologic signs and/or symptoms that would necessitate radiation therapy or surgical decompression in the judgment of the treating clinician.

(3a) centrally located lung tumours that show radiological evidence (CT or MRI) of either:
(i) cavitation or necrosis, or,
(ii) focal invasion or major blood vessels.

(4a) Subjects had received chemotherapy within the previous 4 weeks or had not recovered from adverse events due to chemotherapy. Additional exclusion criteria were previous hemibody external radiotherapy, systemic radiotherapy with radioisotopes within the previous 24 weeks.

(5) previous chemotherapy within a cycle interval, curative radiotherapy within 4 weeks or palliative radiotherapy within 7 days prior to IRPP administration.

(6) prior treatment with any other investigational medicinal product (IMP) within five half-lives of the previous IMP or within 2 weeks, if the previous compound is a mechanism-based molecularly targeted agent whose half-life is not well-characterised and toxicities have not resolved from Grade 2 or higher prior to IRPP administration.

(7) any unresolved NCI-CTCAE Grade 2 or higher toxicity (except alopecia and Grade 2 platinum-therapy related neuropathy) from previous antitumour treatment and/or medical/surgical procedures/interventions.

(8) nephrectomy, renal transplant or concomitant nephrotoxic therapy putting the subject at high risk of renal toxicity during the study as assessed by the investigator.

(9a) history of major thrombotic or clinically relevant major bleeding event in the past 6 months putting the subject at high risk of bleeding during the study as assessed by the investigator (international normalisation ratio (INR) or prothrombin time ≥1.5xULN, unless the subject is receiving anticoagulant therapy).

(10) prior major surgery from which the subject has not sufficiently recovered.

(11a) known allergy to contrast medium product or ^{177}Lu, DOTA, OPS200, OPS301 or any of the excipients of ^{177}Lu-OPS201, as well as to ^{68}Ga-OPS202 or its excipient.

(12a) any condition that precludes the proper performance of PET and/or SPECT scans, CT scans and/or MRI:

(a) subjects who are not able to tolerate the CT contrast agent.

(b) subjects with metal implants or joint prosthesis (depending on the location, if interferes with the PET and/or CT analysis).
Notes: Subjects with metal implants cannot undergo MRI; Subjects with medical devices in situ, which do not overlap with the Volume of Interest in the opinion of the radiologist or dosimetrist or are not expected to interfere with the imaging or interpretation, can be included. The dosimetry team should be informed of the presence of a device in situ.

(c) or any other objects that might interfere with the PET and/or CT analysis.

(d) subjects unable to raise arms for prolonged imaging purposes.

(e) subjects unable to lie still for the entire imaging time.

(f) subjects weighing greater than 130 kg (287 lb).

(13a) subject with history of other malignancy within the past 3 years with the following exceptions: malignancy treated with curative intent and with no active disease and has not received chemotherapy for the last 3 years for these conditions; adequately treated non-melanoma skin cancer without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease; adequately treated breast ductal carcinoma in situ without evidence of disease; prostatic intraepithelial neoplasia without evidence of

prostate cancer at the time of enrolment; adequately treated superficial or in situ carcinoma of the bladder without evidence of disease.

(14) other investigational procedures while participating in this study.

(15a) clinically significant abnormalities on electrocardiogram (ECG) at screening including QTcF >450 msec for males or >470 msec for females at screening or subjects who cannot tolereate high volume load.

(16) pregnant or lactating female. Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 6 months after the last dose of ^{177}Lu-OPS201.

OR

male subject who is unwilling to use acceptable method of effective contraception during treatment and through 6 months after the last dose of ^{177}Lu-OPS201.

(17) subject likely not to be available to complete all protocol-required study visits or procedures and/or to comply with all the required study procedures to the best of the subject and investigator's knowledge.

(18a) history or evidence of psychiatric, substance abuse (except for tobacco smoking), or any other clinically significant disorder, condition or disease (including active known infection with HIV requiring systemic treatment, or known AIDS-related illness, or known active hepatitis B or C infection) that, in the opinion of the investigator or sponsor medical, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

Notes: Female subjects must be either postmenopausal (any female who is age ≥55 years with cessation of menses for 12 or more months or less than 55 years and no spontaneous menses for at least 2 years or less than 55 years and no spontaneous menses within the past 1 year with postmenopausal gonadotropin and oestradiol levels) or permanently sterile, can enter the trial without taking specific contraceptive measures. Female subjects of childbearing potential must have a negative pregnancy test upon entry into this study and agree to use a highly effective method of contraception from Screening until 6 months after the last dose of ^{177}Lu-OPS201;

Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence;

True abstinence, when in line with the preferred and usual lifestyle of the subject, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study participation and for 6 months after the last dose of ^{177}Lu-OPS201. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception; and Male subjects must be either surgically sterile or agree to use a double-barrier contraception method from Screening until 6 months after the last dose of ^{177}Lu-OPS201.

Egg cell and sperm donation are not permitted during the contraception period (up to 2 years after the study).

4.2 Rationale for Inclusion/Exclusion Criteria

Eligibility criteria consists of two parts that define subjects eligible for sstr2 expression screening with ^{68}Ga-OPS202 PET/CT scan first and then those eligible for ^{177}Lu-OPS201 therapy depending on ^{68}Ga-OPS202 PET scan results and matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{11818}F-FDG-PET/CT. The first eligibility check already includes all criteria that apply for ^{177}Lu-OPS201 therapy, thereby excluding ineligible subjects for treatment early on even if their tumour express sstr2.

These criteria define the overall sstr2-positive population and add some clarifications for specific anatomical sites when appropriate. It excludes subjects who have conditions that prevent having readable PET images and/or make the analysis and interpretation of the results difficult or biased. Importantly, some criteria are added to mitigate the risks known with PRRT treatment, especially haematological and renal side effects.

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.8, 5.2.4.1, 6.3, 8.1.6 and 8.1.9.

If a subject decides to withdraw from the study after administration of IIP/IRPP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Sections 5.2.4.1 and 5.2.4.2) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

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

Subjects who withdraw consent for the treatment period may still enter the follow-up period if they wish to.

Subjects may withdraw from the study during the long-term follow-up. The reason for withdrawal will be collected, but this will not be reported as premature withdrawal.

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 samples are kept). If a subject wish to withdraw their consent for biobanking and the samples are still at the investigator site or at Central Laboratory at the time, the investigator must inform the study monitor in writing of the subject's decision and destroy the samples. If the samples are at the sponsor's repository (biobanking vendor), the investigator must inform Ipsen directly using the e-mail address, PPD, mentioning only the subject ID in this e-mail. Ipsen will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the

destruction, which will be forwarded to the investigator. Analyses conducted before the withdrawal will not be affected.

5 STUDY PROCEDURES

5.1 Study Schedule

The phase I schedule of assessment during the study is summarised in Table 5 for the core treatment phase and in Table 6 for the additional cycles. The phase II schedule of assessment will be based on the phase I results and documented as part of a protocol amendment.

Table 5 Schedule of Assessments – Phase I (Core Treatment Phase)

Procedures and assessments	Screening	CORE TREATMENT PHASE																		EOCT or EW [a]	Long-term FU [b]
		Cycle 1									Cycle 2										
	D-28 to D-1	Week 1					W3	W4	W5	W6	W7					W9	W10	W11	W12	W14	
		D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D50 (EOCT)	
Visit window (days)							±1	±1	±1	±1	+28 [c]					±1	±1	±1	±1	+7	±14
Baseline documentation and physical examination																					
Informed consent	x																				
Medical and disease history	x																				
Subject Demographics and Height [ac]	x																				
Body Weight	x	X					x				x					x				x	
Physical Examination Signs and symptoms	x	X					x				x					x				x	
Vital Signs [d]	x	X	x	x			x	x	x	x	x	x	x			x	x	x	x	x	
ECOG performance status	x	X									x									x	
Enrolment																					
Inclusion/Exclusion criteria	x	X																			
Laboratory assessments																					
Haematology [e] and Biochemistry [f]	x	X	x			x	x	x	x	x	x	x			x	x	x	x	x	x	
Urinalysis [g]	x	X	x							x	x	x							x	x	
Pregnancy test [h]	x	X									x									x	
Specific renal safety biomarkers		x [i]		x																x [i]	
Blood sampling for Radiopharmaceutical PK [j]		X	x	x	x	x					x	x	x	x	x						
OPS201 PK blood [k]		X	x	x																	
Urine sampling for radioactivity analysis [l] and OPS201 PK[m]		X	x	x																	

Procedures and assessments	Screening	CORE TREATMENT PHASE																		EOCT or EW [a]	Long-term FU [b]
		Cycle 1									Cycle 2										
	D-28 to D-1	Week 1					W3	W4	W5	W6	W7					W9	W10	W11	W12	W14	
		D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D50 (EOCT)	
Visit window (days)							±1	±1	±1	±1	+28 [c]					±1	±1	±1	±1	+7	±14
Hypothalamic-pituitary-adrenal axis, testicular and pancreatic biomarkers (hormone analysis) [n]		X									x									x	
DNA repair capacity in blood (Selected centres)		X	x								x									x	
DNA-DSB in peripheral lymphocytes [o]		X	x	x	x						x	x	x	x							
Biobanking (optional)		x [p]									x [p]									x [p]	
Germinal mutation in blood [ab]		x																			
Investigational Radiopharmaceutical Product Administration (IRPP)																					
^{177}Lu-OPS201 + amino acid solution		x									x										
Tumour assessments																					
^{68}Ga-OPS202 PET/CT imaging [s]	x																			x	
ceCT/MRI [t]	x										x									x	x
18F-FDG-PET/CT [u]	x																			x	
Tumour Biopsy [v]	x																			x	
Dosimetry assessments																					
SPECT/CT scan [w]		x	x	x	x	x					x	x	x	x	x						
Whole-body SPECT/CT scan [x]		x	x	x	x	x					x	x	x	x	x						
Other clinical assessments																					
EQ-5D-5L and EORTC QLQ-C30 [y]		x																		x	
AEs [z]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prior and Concomitant medication/procedure[aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Further antitumour treatment																					x
Procedures and assessments	**Screening**	**CORE TREATMENT PHASE**																		**EOCT or EW [a]**	**Long-term FU [b]**
		Cycle 1									**Cycle 2**										
	D-28 to D-1	Week 1					W3	W4	W5	W6	W7					W9	W10	W11	W12	W14	
		D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D1	D2	D3	D4 D5	D7 D8	D15	D22	D29	D36	D50 (EOCT)	
Visit window (days)							±1	±1	±1	±1	+28 [c]					±1	±1	±1	±1	+7	±14
ECG (12-lead) [q]	x	x									x									x	
6-hour ECG (Holter) [r]		x									x										

[a] The End of Core Treatment (EOCT) visit, planned at Day 50 of Cycle 2, will take place for all subjects, even if they can benefit from additional cycles. In such a case, EOCT visit and Day 1 of first additional cycle can occur on the same day. The Early Withdrawal (EW) visit will take place within 14 days after the decision to withdraw a subject early. Afterwards, the subject will enter the follow-up period.

[b] Follow-up visits will take place every 3 months (±14 days) for 2 years. It starts after the cycle of the last IRPP (^{177}Lu-OPS201) administration. Subjects will be monitored for survival. Tumour imaging will also take place for the subjects who discontinued study treatment before disease progression and who have not withdrawn consent for this long-term follow-up.

[c] In case of toxicity management requiring a delay, the next ^{177}Lu-OPS201 treatment administration will be delayed to up to 4 weeks.

[d] Supine and standing systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate. For the day of infusion: Prior to infusion and at infusion completion (0 minutes), 30±5 minutes, 60±10 minutes, 4 hours ±10 minutes after the end of infusion.

[e] At screening only: haematology should be repeated within 48h before first infusion. Blood haematology: RBC count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count. See also Section 8.2.

[f] At screening only: biochemistry should be repeated within 48h before first infusion. Blood biochemistry: urea, uric acid, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin and total protein, total cholesterol, triglycerides, fasting glucose, C-reactive protein (CRP). eGFR will be calculated based on serum creatinine levels using MDRD formula. See also Section 8.2.

[g] Urinalysis includes pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leucocytes, glucose; proteinuria will be performed with dipsticks, in case of positivity, a proteinuria/24h will be performed. See also Section 8.2.

[h] Serum pregnancy test will be performed at the screening visit and EOCT. A urine pregnancy test will be performed on Day 1 of each treatment cycle before IRPP infusion.

[i] Predose DNA repair capacity in blood at Day 1 and specific renal safety biomarkers (alpha-glutathione S-transferase (GST), glutathione S transferase P1 (GSTP1), kidney injury molecule-1 (KIM-1) antigen, clusterin, cystatin-C, calbindin, beta-2 microglobulin, creatinine) at Day 1 or at D-1 (before administration day). See also Section 8.2.

[j] Activity measured on blood samples (n=10 per cycle) before the infusion (baseline), at the end of ^{177}Lu-OPS201 infusion (0) and at 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes), 24±2 hours, 48±2 hours, 72 to 96 hours and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion (Cycle 1 and 2).

[k] OPS201 plasma levels in blood samples (n=10 samples) collected at Cycle 1 at the following time points: before the infusion (baseline), at the end of infusion (0) and at 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes), 6 hours (±30 minutes), 8 hours (±30 minutes), 24±2 hours and 48±2 hours post-infusion of ^{177}Lu-OPS201

[l] Activity measured on urine collected over the first 48 hours post-infusion at the following time intervals: 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours (0 to 4 and 4 to 8 hours only in US sites) post-infusion, with an initial void collection shortly before the infusion (0 hour) and a final collection 48 hours after administration of ^{177}Lu-OPS201 (Cycle 1 only).

[m] OPS201 urine levels in urine collected at Cycle 1 at the following time intervals: 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours (0 to 4 and 4 to 8 hours only in US sites) post-infusion, with an initial void collection shortly before the infusion (0 hour) and a final collection 48 hours after administration of ^{177}Lu-OPS201 (Cycle 1 only).

[n] Hypothalamic-pituitary-adrenal axis biomarkers sample for hormone analysis (sstr2 organ expressing) should be taken predose at the closest to 8.00 am and includes analysis of Pituitary/Adrenal axis (FT4, TSH, LH, FSH, cortisol, IGF-1) Pancreatic function (glucose, glycosylated haemoglobin (HbA1c)) and Testicular function (testosterone, Inhibin B; SHBG). Protocol allows the collection of those pre dose samples at D-1 before the administration day (D1). See also Section 8.2.

[o] DNA-DSB measured in lymphocytes (n=6 per cycle) before the infusion (baseline), at 1 hour (±10 minutes), 4 hours (±30 minutes), 24 hours (±2 hours), 48 (±2 hours) and 72 to 96 hours after the end of ^{177}Lu-OPS201 infusion (Cycle 1 and Cycle 2)

[p] Biobanking samples (serum and whole blood) for exploratory biomarkers should be taken predose. It can only be obtained after signature of optional biobanking informed consent form. Protocol allows the collection of those pre-dose samples at D-1 before the administration day (D1).

[q] Single 12-lead ECG to be recorded in the supine position after at least 5 minutes of rest at screening, at Day 1 before the infusion (baseline) and at EOCT visit.

[r] Starting before study drug administration, a 6-hour 3-lead continuous Holter ECG will be recorded.

[s] ^{68}Ga-OPS202 imaging will only be acquired once inclusion/exclusion criteria are confirmed (Biopsy can be done after ^{68}Ga-OPS202 PET eligibility has been confirmed, provided the subject's agreement to undergo biopsy was obtained before ^{68}Ga-OPS202 PET). All images will be sent to the ICL. ceCT/MRI is to be performed with the ^{68}Ga-OPS202 PET scan unless it was done with the 18F-FDG-PET or alone within 2 weeks. In this case low dose CT could be performed with ^{68}Ga-OPS202 PET.

[t] The ceCT/MRI imaging including brain will take place 6 weeks (± 3 days) after each administration of ^{177}Lu-OPS201 using the same imaging method.

[u] ^{18}F-FDG-PET whole-body including brain unless performed within 28 days prior to the first administration. All images must be sent to the central ICL.

[v] In case archival tissue from a biopsy done in the 1 month prior to consent and after the end of previous treatment this can be used for sstr2 IHC, tumour biomarkers, tumour microenvironment analysis, transcriptomics. If not, a baseline biopsy has to be taken from the primary or metastatic lesion. If possible, the biopsy should be taken from an accesible lession which is positive for sstr2 with ^{68}Ga-OPS202 scan following the eligibility criteria #10 (Section 5.2.1) and can be accomplished with reasonable safety. An optional post-treatment biopsy can also be performed during EOCT visit. In selected centres as for DNA repair capacity in blood, if tumour biopsy is >5 mm^3, then 5 mm^3 will be fixed for tumour microenvironment analysis, the rest will be frozen for DNA repair capacity assessment.

[w] Tumour and organs uptake using Single Photon Emission CT (SPECT/CT) at Cycles 1 and 2 at 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, at 72 to 96 and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion. At the timepoint between 16 to 24 hours, SPECT/diagnostic CT will be performed (no contrast agent). For all other time points, SPECT/low dose CT will be performed.

[x] Whole-body (planar scintigraphy) scan will be done at Cycles 1 and 2 at 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, at 72 to 96 and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion. 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).

[y] For the phase II only. Subjects will complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires at the clinic prior to ^{177}Lu-OPS201 infusion on Day 1 of Cycle 1 and at EOCT.

[z] Subjects must be followed for AEs from the time they signed the informed consent form until the EOCT/EW or EOAC. All study treatment related toxicities will be followed by the investigator until they have resolved.

[aa] Concomitant medications and treatments with doses and indications will be recorded from 60 days prior to the IRPP administration. Once the subject has withdrawn from the study, concomitant medications and treatments should be recorded until the EOCT/EW or EOAC or until all study treatment related toxicities have resolved, whichever is the later.

[ab] Blood sample before infusion.

[ac] Race and ethnicity will be recorded if allowed per local regulations.

Table 6 Schedule of Assessments – Phase I (Additional Cycles)

Procedures and assessments	ADDITIONAL CYCLES									EOAC or EW [a]	Long-term FU [b]
	Cycle 3, 4, 5 and 6										
	Week 1				W2	W3	W4	W5	W6	W8	
	D1	D2	D3	D4-5	D7-8	D15	D22	D29	D36	D50	
Visit window (days)	+28 [c]					±1	±1	±1	±1	+7	±14
Physical examination											
Body Weight	x					x				x	
Physical Examination Signs and symptoms	x					x				x	
Vital Signs [d]	x	x	x		x	x	x	x	x	x	
ECOG performance status	x									x	
Laboratory assessments											
Haematology [e] and Biochemistry [f]	x	x			x	x	x	x	x	x	
Urinalysis [g]	x	x								x	
Urine Pregnancy test	x									x	
Specific renal safety biomarkers										x	
Blood sampling for Radiopharmaceutical PK [h]	x	x	x	x	x						
ECG (12-lead) [i]	x									x	
Investigational Radiopharmaceutical Product Administration											
^{177}Lu-OPS201 + amino acid solution	x										
Tumour assessments											
ceCT/MRI [j]	x									x	x
Dosimetry assessments											
SPECT/CT scan [k]	x	x	x	x	x						
Whole-body (planar scintigraphy) scan [l]	x	x	x	x	x						
Other clinical assessments											
AEs [m]	x	x	x	x	x	x	x	x	x	x	x
Prior and Concomitant medication/procedure [n]	x	x	x	x	x	x	x	x	x	x	
Further antitumour treatment											x

[a] The End of Additional Cycles (EOAC) visit will take place within 14 days after the end of the last cycle. The Early Withdrawal (EW) visit will take place within 14 days after the decision to withdraw a subject early. Afterwards, the subject will enter the follow-up period.

[b] Follow-up visits will take place every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first. It starts after the cycle of the last IRPP (^{177}Lu-OPS201) administration. Subjects will be monitored for survival. Tumour imaging (ceCT/MRI) will also be performed every 3 months during the follow-up period. Tumour imaging will also take place for the subjects who discontinued study treatment before disease progression and who have not withdrawn consent for this long-term follow-up.

[c] In case of toxicity management requiring a delay, the next treatment administration will be delayed to up to 4 weeks.

[d] Supine and standing systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate. For the day of infusion: Prior to infusion and at infusion completion (0 minutes), 30±5 minutes, 60±10 minutes, 4 hours ± 10 minutes after the end of infusion.

[e] Haematology: RBC count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count. See also Section 8.2.

[f] Blood biochemistry: urea, uric acid, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin and total protein, total cholesterol, triglycerides, fasting glucose, C-reactive protein (CRP). eGFR will be calculated based on serum creatinine levels using MDRD formula. See also Section 8.2

[g] Urinalysis includes pH, protein, ketones, bilirubin, urobilinogen, blood, nitrites, leucocytes, glucose; proteinuria will be performed with dipsticks, in case of positivity, a proteinuria/24h will be performed. See also Section 8.2.

[h] Activity measured on blood samples (n=10 per cycle) before the infusion (baseline), at the end of ^{177}Lu-OPS201 infusion (0) and at 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes), 24±2 hours, 48±2 hours, 72 to 96 hours and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion (for each additional cycle).

[i] Single 12-lead ECG to be recorded in the supine position after at least 5 minutes of rest at screening, at Day 1 before the infusion (baseline) and at EOCT visit.

[j] Imaging will take place 6 weeks (± 3 days) after each administration of ^{177}Lu-OPS201 using the same imaging method. There will be also imaging done during the follow up period (see Section 5.2.4.2)

[k] Tumour and organs uptake using Single Photon Emission CT (SPECT/CT) at each additional cycle at 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, at 72 to 96 and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion. At the timepoint between 16 to 24 hours, SPECT/diagnostic CT will be performed. For all other time points, SPECT/low dose CT will be performed.

[l] Whole-body (planar scintigraphy) scan will be performed at 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, at 72 to 96 and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion. 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).

[m] Subjects must be followed for AEs from the time they signed the informed consent form until the EOCT/EW or EOAC. All study treatment related toxicities will be followed by the investigator until they have resolved.

[n] Concomitant medications and treatments with doses and indications will be recorded from 60 days prior to the IRPP administration. Once the subject has withdrawn from the study, concomitant medications and treatments should be recorded until the EOCT/EW or EOAC or until all study treatment related toxicities have resolved, whichever is the later.

5.2 Study Visits

The study procedures and assessments for phase I are summarised in Table 5 and Table 6.

A signed and dated informed consent form (ICF) will be obtained before screening procedures.

5.2.1 Procedures for Screening and Enrolment

Eligibility should be checked before proceeding to the investigational Imaging with ^{68}Ga-OPS202 PET/CT.

Avid lesions identified by ^{68}Ga-OPS202 PET/CT scan will be interpreted as sstr2-positive if the uptake is 1.5-fold or greater than the non-tumour liver and lung tissue is noted and confirmed by central reading. Only subjects with at least two avid lesions of ≥ 20 mm on longest diameter on ^{68}Ga-OPS202 PET/CT scan will be considered eligible for treatment with ^{177}Lu-OPS201. Furthermore, it is required ≥50% matching between the lesions detected on ^{68}Ga-OPS202-PET/CT and on ^{18}F-FDG-PET/CT as confirmed by central reader.

If an ^{18}F-FDG-PET or ceCT/ceMRI was done within 28 days prior to first administration of ^{177}Lu-OPS201, the procedure/s should only be repeated if the image/s are unreadable. If a tumour biopsy was obtained within 28 days prior to screening, the procedure/s should not be repeated. Evaluations obtained as part of routine medical care and performed during the screening period may also be used in place of the study specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.

Subjects will be offered to participate to an optional research biobanking program. Subjects who agree to participate will be requested to sign a separate informed consent.

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

Subjects could be re-screened upon sponsor's approval (e.g. laboratory value back to allowed range within an acceptable timeframe).

Following confirmation of eligibility for the treatment, subjects will be considered as enrolled and allocated to one of the cohorts specified in Figure 5.

Each investigator will also maintain a record of all subjects screened into the study (i.e. who signed the informed consent form). In the event that the subject does not receive ^{68}Ga-OPS202 or ^{177}Lu-OPS201, the primary reason will be recorded.

5.2.2 Procedures Before Study Treatment (Day 1 of Each Treatment Cycle, Pre-Dose)

The following procedures may not be performed at Baseline on Day 1 of the study, prior to the administration of study treatments if an acceptable screening assessment was performed within 7 days prior to the start of study treatment:

- Haematology and biochemistry
- Urinalysis
- Pregnancy test
- Body weight

5.2.3 Procedures During Study Treatment (Day 1 Post Dose of Each Treatment Cycle)

Procedures during Cycle 1 and 2 and additional cycles are summarised in Table 5 and Table 6, respectively.

Subject may be hospitalised from Day 1 to Day 3 at the discretion of the investigator.

The subjects must return to the study centre for further evaluations per the Schedule of assessment

5.2.4 Procedures After Study Treatment

5.2.4.1 End of Study Visit (EOCT, EOAC or Early Withdrawal Visit)

Subjects who participate in the study in compliance with the protocol for at least two cycles of IRPP administration will be considered to have completed the study.

Subjects may also withdraw from the study at any time if they meet any of the criteria described in Section 3.8.

For subjects who complete the study, final evaluations will be performed within 6 weeks after the last IRPP administration; for those who withdraw prematurely from the study, final evaluations should be performed within 14 days.

Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored by the investigator as described in Section 8.1.4 and Section 8.1.2.4, respectively.

5.2.4.2 Follow up Visits

After the EOCT/EOAC or withdrawal visits, subjects will enter the follow-up period. Follow-up visits will take place every 3 months until 24 months, disease progression, death or withdrawal of full consent, whichever occurs first. It starts after the cycle of the last IRPP (^{177}Lu-OPS201) administration. Subjects will be monitored for survival. Tumour imaging (ceCT/MRI) will also be performed every 3 months during the follow-up period.
Subjects will be monitored for survival during 2 years after their withdrawal visit. Tumour imaging (ceCT/ceMRI) will also take place (every 3 months) for the subjects who discontinued study treatment before disease progression and who have not withdrawn consent.
Antitumour treatment for the studied disease will be recorded during this follow-up period.

5.2.5 Unscheduled Visits

Unscheduled visits or assessments may be necessary at any point during the treatment period to assess individual safety or tolerability. For example, laboratory assessments should be performed as clinically indicated during the study, tumour assessment could be performed whenever disease progression is suspected. Should an unscheduled visit or procedure listed in the schedule of assessment be performed during the study, the data will be recorded in the eCRF.

5.3 Tumour Imaging and Dosimetry

The ICL will provide further technical instructions in separate image acquisition guidelines for the study. All the images will be sent to the central ICL for an independent review within 24 hours (1 business day) of acquisition.

- **^{68}Ga-OPS202 PET Imaging (Whole body)**: acquired at screening and 6 weeks after second administration of ^{177}Lu-OPS201 (Cycle 2). The eligibility of the subjects will be assessed centrally on screening images. The central reading results will be used for the analysis of the imaging efficacy endpoints. CeCT/MRI for brain should be acquired with the ^{68}Ga-OPS202 PET at screening.

- **ceCT/ceMRI**: acquired at screening and 6 weeks after each administration of ^{177}Lu-OPS201 as well as every 3 months during the follow-up period. For each subject, the same imaging methods should be used throughout the study. The ceCT is acquired

either with ^{68}Ga-OPS202 or ^{18}F-FDG PET or separately, but should not be repeated for the same endpoint; a low dose CT could be done with each PET if not coupled with ceCT.

- **^{18}F-FDG-PET (Whole body)**: acquired at screening and 6 weeks after second administration of ^{177}Lu-OPS201 (Cycle 2).

- **SPECT/CT Scan**: After the end of each ^{177}Lu-OPS201 infusion: at 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, 72 to 96 and 144 to 168 hours.

- **Whole-body (planar scintigraphy) Scan**: 2 to 4 hours, 16 to 24 hours, 40 to 48 hours, 72 to 96 and 144 to 168 hours after the end of ^{177}Lu-OPS201 infusion.

The total radiation dose per subject for a two cycles treatment period is summarised in Table 7.

Table 7 Total Effective Dose (in mSv) per Subject for a Two Cycles Treatment Period

Procedure	Screening	Cycle 1	Cycle 2	EW/EOCT Visit	Total
^{68}Ga-OPS202 [a]	4	NA	NA	4	8
ceCT [b]	15 - 30	15 - 30	15 - 30	15 - 30	60 - 120
MRI [c]	0	0	0	0	0
^{18}F-FDG-PET [d]	6.3	NA	NA	6.3	12.6
SPECT/CT low dose [e]		4 (x4 scans)	4 (x4 scans)		32
SPECT/diagnostic CT [e]		6 (1 scan)	6 (1 scan)		12
					120 - 180

Abbreviations: ceCT=contrast enhanced computed tomography; EOCT=end of core trial; EW=early withdrawal; FDG=fluorodeoxyglucose; MRI=magnetic resonance imaging; N=not applicabale ; PET=positron emitting tomography.
a The phase I study ^{68}Ga-OPS202, the calculated effective dose for an injection of 150 MBq (4 mCi) of ^{68}Ga-OPS202 was 3.6 mSv. The upper end of the activity is 200 MBq which equates to about 4 mSv.
b Sources: Huang 2009, Christner 2010, Pearson 2014.
c MRI has no radioactive dosing, only strong magnetic fields.
d Source : Huang 2009.
e Calculated from VirtualDose. There is no radiation from the SPECT, but just from the CT scan (the SPECT uses the radiation being emitted from the therapeutic ^{177}Lu-OPS201).

Confirmation of eligibility and details of the avid lesions to be further followed by SPECT and dosimetry conducted by the ICL will be provided to the site. The other results of the central imaging review or reads will not be provided to the subject nor to the investigational site personnel. Efficacy reads will be conducted by the central ICL and all subject management will be conducted by the principal investigator.

5.4 Laboratory Assessments

The following samples will be analysed locally:

- Standard haematology and biochemistry
- Urinalysis
- Pregnancy test (serum and urine)
- Radiopharmaceutical PK urine (gamma-counting)
- Radiopharmaceutical PK blood (gamma-counting)

The following samples will be sent for central analysis:

- Hypothalamic-pituitary-adrenal axis, testicular and pancreatic biomarkers

- OPS201 PK blood
- OPS201 PK urine
- DNA repair capacity in blood (in selected centres only)
- DNA-DSB in peripheral lymphocytes
- Specific renal safety biomarkers (alpha-glutathione S-transferase (GST), glutathione S-transferase P1 (GSTP1), kidney injury molecule-1 (KIM-1) antigen, clusterin, cystatin-C, calbindin, beta-2 microglobulin, creatinine)
- Tumour microenvironment biomarkers
- Biopsies
- Biobanking (optional)

The total volume of blood drawn for all evaluations throughout this study is approximately 281.5 mL for each subject participating in the core trial (two first cycles). The detail of the blood samples collected at Screening and over the two first cycles of ^{177}Lu-OPS201 is provided in Table 8.

Table 8 Blood Samples Collected at Screening and over First Two Cycles

Test	Number of Samples	Volume per Sample
PK ^{177}Lu-OPS201	20	2 mL
PK OPS201	10	2 mL
DNA-DSB	12	4 mL
DNA repair	4	8 mL
Haematology	16	2 mL
Biochemistry	16	5 mL
Hypothalamic-pituitary-adrenal-axis hormones and other biomarkers	3	9 mL
Germinal mutation in blood	1	2.5 mL
Total volume		**281.5 mL**

An additional 19.5 mL of blood will be collected from subjects who have signed the optional biobanking informed consent for biobanking; this will be taken at Day 1 (or Day -1) of Cycle 1 before infusion and at Day 1 of Cycle 2 before infusion and at EOCT/EOAC/EW for a total of 58.5 mL. For subjects who have biobanking samples, a total of 340 mL blood will be collected.

6 IMAGING AND TREATMENT OF SUBJECTS

6.1 Investigational Imaging/Medicinal Product Preparation Storage and Accountability

6.1.1 Investigational Imaging/Radiopharmaceutical Product Storage and Security

6.1.1.1 ^{68}Ga-OPS202

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

6.1.1.2 ^{177}Lu-OPS201

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

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.

6.1.1.3 Spillage

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

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

See Section 9.2 for requirement of whole-body scan in case of spillage during infusion.

6.1.2 Investigational Imaging/Radiopharmaceutical Product Preparation

6.1.2.1 ^{68}Ga-OPS202

The investigator, or an approved representative (e.g. pharmacist), will ensure that each radiolabelling kit is reconstituted, radiolabelled and dispensed by qualified staff members.
The treatment is provided as a sterile two-vial radiolabelling kit (one kit per subject dose) constituted of:

- freeze-dried powder containing 50 µg non-radiolabelled precursor OPS202 and excipients (Vial A) and
- the solvent for reconstitution (Vial B) to be used prior to radiolabelling.

The final radiolabelled IIP (^{68}Ga-OPS202) will be prepared, up to 3 hours prior to administration, in the local radiopharmacy, in a two-step aseptic compounding process,

according to Good Radiopharmaceutical Practice (GRPP) per EANM guidelines and according to national regulations on radiopharmaceuticals preparation:

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

^{68}Ga-radiolabelling yields the IIP ^{68}Ga-OPS202 as a solution for injection. After QC sampling, QC testing and release, the volume to be administered to the subject is withdrawn from the IIP vial, containing up to 45 µg OPS202. This volume is determined to obtain the target radioactivity at the time of administration, taking into account the decay of ^{68}Ga.

6.1.2.2 ^{177}Lu-OPS201

The IRPP is supplied as a 20-mL sterile solution for infusion.

6.1.3 Investigational Imaging/Radiopharmaceutical Product Accountability

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 radiolabelling kit, treatment or any other study-related material are correctly received by a responsible person.
- 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.
- The destruction of used and unused study treatment radiolabelling kit, IRPP, IIP and any other study related material should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. The study treatment will be destroyed on site.
- All radiolabelling kit, IIP, IRPP and any other study related material is to be accounted for on the IMP accountability log provided by the sponsor.

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, the quantity, the radioactivity and date of dispensing. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms.

6.2 Investigational Imaging/Radiopharmaceutical Product Administered

At screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will receive a single dose of ^{68}Ga-OPS202 (IIP), of up to 45 µg peptide, with a radioactivity of between 150 to 200 MBq.

Then, in phase I, subjects deemed eligible for treatment with ^{177}Lu-OPS201 based on ^{68}Ga-OPS202 tumour uptake will receive:

- In the radioactivity escalation: two cycles of ^{177}Lu-OPS201 separated by 6 weeks (+4 week per cycle in case of AEs that need to be adequately recovered) of 300 µg (±15%) OPS201 with activities ranging from 4.5 to 7.4 GBq (±10%) for the loading dose and 3 to 5.5 GBq (±10%) for the maintenance dose.

- In the peptide mass dose evaluation phase: two cycles of ^{177}Lu-OPS201 separated by 6 weeks (+4 week per cycle in case of AEs that need to be adequately recovered) of 700 µg (±15%) OPS201 with activities ranging from 4.5 to 7.4 GBq (±10%) for the loading dose and 3 to 5.5 GBq (±10%) for the maintenance dose.

The radioactivity is measured before and after the administration of IIP and IRPP to the subject; the decay-corrected difference between these two measurements (in MBq and GBq, respectively) corresponds to the radioactivity administered to subject.
The IIP ^{68}Ga-OPS202 is administered as a slow bolus intravenous injection and the IRPP ^{177}Lu-OPS201 as an intravenous infusion over 120 minutes (at the investigator's discretion - see details in Section 6.2.2).
Radioactivity and peptide mass doses in phase II will depend on the results from phase I.

6.2.1 ^{68}Ga-OPS202

^{68}Ga-OPS202 is an imaging radiopharmaceutical with three main components, namely:

- OPS200, an antagonist somatostatin analogue that binds to sst2
- NODAGA, a chemical chelator moiety and
- ^{68}Ga, a positron-emitting radionuclide with a half-life of 68 minutes.

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

There are no fasting conditions, nor food restrictions that should apply when administering ^{68}Ga-OPS202 to the subject.

To determine tumour uptake at Screening visit, subjects will receive a single i.v. injection of IIP (^{68}Ga-OPS202) administered over 1 minute prior to a PET/CT scan.

6.2.2 ^{177}Lu-OPS201

^{177}Lu-OPS201 is a therapeutic radiopharmaceutical with three main components, namely:

- OPS200, an antagonist somatostatin analogue that binds to sstr2
- DOTA, a chemical chelator moiety and
- ^{177}Lu, a beta-emitting radionuclide with a half-life of 6.7 days

The IRPP (20 mL of ^{177}Lu-OPS201) will be administered once per cycle as 300 µg (±15%) or 700 µg (±15%) of OPS201 by an i.v. infusion at a rate of 10 mL/h over 120 minutes for ^{177}Lu-OPS-201. 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: The rate of infusion can be adjusted based on recommendations from DRB.

Activities will range from 4.5 to 7.4 GBq for the loading dose and 3 to 5.5 GBq for the maintenance dose. The IRPP will be co-infused with amino acid solution (see Section 6.3). 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 6.3.2 and Section 6.3.3). Appropriate treatment should be administered should an infusion-related reaction occur including somatostatin analogues.

There are no fasting conditions, nor food restrictions that should apply when administering ^{177}Lu-OPS201 to the subject.
The same venous access for IRPP and amino acid solution administration will be used. Infusion should be done into the contra-lateral arm used for the PK sampling. Subjects with breast

surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm.

6.3 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a subject within 60 days before IIP administration or during IIP/IRPP administration will be indicated in the eCRF. Dose and generic name or tradename will be indicated.

The following concomitant medications are not permitted during this study:

- nephrotoxic compounds as assessed by the investigator
- any tumour-targeted therapy (e.g. chemotherapy, radiotherapy)

^{177}Lu-OPS201 is investigated in the current study as monotherapy; thus, any tumour-targeted therapy (e.g. chemotherapy, radiotherapy) are not allowed during the study. The investigator may withdraw the subject in order to administer another tumour-targeted therapy if deemed necessary for the health of the subject.

Subjects with brain metastasis who are receiving high doses of glucocorticosteroids must not be enrolled in the study (see Section 4.1). Likewise, investigator should consider withdrawing subjects from ^{177}Lu-OPS201 treatment should the administration of high doses of glucocorticosteroids be needed for the management of any condition, as these drugs may induce down-regulation of sstr2. Glucocorticosteroids should be avoided as preventive anti-emetic treatment. In case prior treatment provided for nausea and vomiting is not efficient, a single dose of corticosteroids can be used.

The potential of OPS201 to be associated with drug-drug interactions has not been established. It is anticipated that the major route of excretion will be via the kidneys and so medications which might affect renal function should be avoided or used with due caution as assessed by the investigator. These medications include but are not limited to the following.

Drugs causing prerenal damage:

- Drugs that cause excessive gastrointestinal losses, either through diarrhoea or vomiting, also cause volume depletion and may precipitate acute kidney injury (AKI).
- Non-steroidal anti-inflammatory drugs (NSAIDs), even in short courses, can cause AKI as a result of renal underperfusion.
- Angiotensin-converting enzyme (ACE) inhibitors can also cause a deterioration in renal function. However, this is a problem only in patients with compromised renal perfusion, particularly those with renal artery stenosis.
- Care should be taken when an ACE inhibitor and NSAID are prescribed together, as this combination may precipitate an acute deterioration in renal function.

Drugs causing intrarenal damage:

- Intrarenal damage may result in a direct toxic effect on the kidneys or hypersensitivity reactions.
- Most drugs that cause damage within the kidneys do so as a result of hypersensitivity reactions, which involve either glomerular or interstitial damage.
- Drugs that have been reported to cause glomerulonephritis include penicillamine, gold, captopril, phenytoin and some antibiotics, including penicillins, sulfonamides and rifampicin.
- Drugs that may cause interstitial nephritis include penicillins, cephalosporins, sulfonamides, thiazide diuretics, furosemide, NSAIDs and rifampicin.

- There are a number of drugs that cause direct toxicity to the renal tubules (acute tubular necrosis) - eg, aminoglycosides, amphotericin and ciclosporin.

Drugs causing postrenal damage (urinary tract obstruction):

- High-dose sulfonamides, acetazolamide or methotrexate may cause crystalluria and could therefore cause urinary tract obstruction.
- Anticholinergics (eg, tricyclic antidepressants), and alcohol may cause urinary tract obstruction due to retention of urine in the bladder.

Other nephrotoxic drugs:

- Cephalosporins: cephaloridine, one of the first cephalosporins introduced, has been associated with direct renal toxicity and is no longer in clinical use. Other cephalosporins are much less likely to produce renal damage but third-generation cephalosporins (eg, cefixime) have (very rarely) been reported to cause nephrotoxicity.
- Analgesics:
  - NSAIDs may cause AKI due to hypoperfusion and interstitial nephritis, as well as analgesic nephropathy (chronic interstitial nephritis and papillary necrosis).
  - Analgesic nephropathy has been most commonly seen with combination analgesic products that contain aspirin and/or paracetamol.
  - Analgesic nephropathy is one of the few preventable causes of chronic kidney disease. Discontinuation of the drugs often results in stabilisation or even improvement in renal function but continued use leads to further renal damage.
- Lithium: serum levels of lithium consistently above the therapeutic range have been associated with development of a nephrogenic diabetes insipidus.

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

- Antiemetic premedication (oral or iv administration) should be administered 30 minutes before starting the amino acid solution. Despite the preventive treatment, a subject may suffer from nausea. The adverse event should be managed by hydrating the subject with normal saline and possibly by repeating antiemetic administrations of different pharmacological class.
- Infusion related reactions (IRR) should be managed as per local guidelines or institutional protocols and according to their grading. If the time to symptom resolution does not allow to resume the IRPP infusion within the 60 minutes time span, the IRPP will be stopped. See also adverse events of special interest (Section 8.1.3).

6.3.1 Amino acid infusion: renal protection

The role of amino acid solution is to protect subject's kidneys during PRRT by blocking ^{177}Lu-OPS201 reabsorption and preventing nephrotoxicity of the radioactive element.

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 (Bodei 2013) a solution of 25 g lysine and 25 g arginine in 2 L saline is recommended to be infused concomitantly with the PRRT administration over 4 hours (or up to 6 hours in exceptional cases), starting 30-60 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 adverse events or subjects' intolerance of the high-volume load in a short time. In case of severe

nausea or vomiting during amino acid solution infusion, an anti-emetic of a different pharmacological class can be administered.

Sites experienced in PRRT treatment can use Ipsen's amino acid solution (OPS301, which could be provided during the study) or their established amino acid solution, preferably commercialised product covered by the recommendations of the joint IAEA, EANM and SNMMI practical guidance on PRRT in NETs. The exact formulation must be documented in the eCRF.

OPS301 is an amino acid solution made of arginine and lysine (1.25% w/v each). The solution is supplied as a 500-mL sterile solution for infusion. A maximum of four bottles are used per subject administration (equivalent to 2 L).

6.3.2 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). 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.

6.3.3 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.

6.4 Lifestyle Restrictions/Recommendations

There are no alcohol, diet or smoking restrictions besides restrictions already presented in the exclusion criteria. Investigator will be advised to ensure appropriate hydration of subjects during urine collection periods.

6.5 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.

Administration compliance will be assessed by the trained staff/nurse performing the injection in case of incomplete injection of the IIP or IRPP, the residual activity in the syringe should be recorded in the eCRF.

7 ASSESSMENT OF PHARMACODYNAMICS/EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 5 and Table 6.

7.1 Phase I

7.1.1 Secondary Tumour Activity Endpoints and Evaluations

Secondary tumour activity endpoints and evaluations planned in phase I are summarised in Table 9. All tumour endpoints will be evaluated by a central ICL.

Table 9 Secondary Tumour Activity Endpoints and Evaluations in Phase I (Core Treatment)

Measure	Timepoints	Variable	Endpoint
Tumour size (longest diameter)	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Tumour response according to RECIST v1.1	ORR BOR DCR PFS
Tumour size (longest diameter)	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour response according to mGa-RECIST; Metabolic tumour response by ^{18}F-FDG-PET using PERCIST v1.0 and ^{68}Ga-OPS202 by mGa-PERCIST	ORR BOR
Tumour volume	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Mean change (%) in tumour volume assessed by Volumetric CT (or MRI)	% change from baseline in tumour volume
Event of death	1 and 2 years	Death count	OS
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour-to-background ratio by ^{18}F-FDG-PET using PERCIST v1.0	Quantitative changes in tumour-to-background ^{18}F-FDG-PET uptake
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	sstr2 targeted tumour uptake by ^{68}Ga-OPS202 PET/CT.	Changes in tumour uptake on ^{68}Ga-OPS202 PET/CT
SUV_{max} and SUV_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	^{68}Ga-OPS202 uptake and ^{177}Lu-OPS201 therapy response	Change in ^{68}Ga-OPS202 uptake on PET scan in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and BOR

Measure	Timepoints	Variable	Endpoint
SUV_{max} and SUV_{mean}	Screening[a] for ^{68}Ga-OPS202 PET/CT; Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Uptake on ^{68}Ga-OPS202-PET/CT and ^{177}Lu-OPS201 therapy response (using ceCT/MRI – RECIST v1.1)	Correlation between change (%) in tumour uptake on ^{68}Ga-OPS202 PET/CT at screening[a] with tumour response to ^{177}Lu-OPS201 therapy.
Lesion count	For ^{68}Ga-OPS202 at screening For ^{177}Lu-OPS201 at 24 hours after first administration (Cycle 1)	Uptake on ^{68}Ga-OPS202-PET/CT and uptake on ^{177}Lu-OPS201 SPECT/CT	Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT

Abbreviations: BOR=Best overall response; ce= Contrast enhanced; CT=Computed tomography; DCR=Disease control rate; FDG=Fluorodeoxyglucose; mGa= Modified gallium; MRI=Magnetic resonance imaging; ORR=Objective response rate; OS=Overall survival; PERCIST=Positron emission tomography response criteria in solid tumours; PFS= Progression free survival; PET= Positron emission tomography; RECIST=Response evaluation criteria in solid tumours; SUL=SUV normalised by lean body mass; SUV=Standardised uptake volume.
a. Screening=Baseline scan

7.1.2 Methods and Timing of Assessing, Recording and Analysing Anti-Tumour Activity Data

Methods for assessing efficacy data are described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 15 and methods of analyses are discussed in Sections 11.2 and 11.3.

7.1.2.1 Imaging Assessments and Evaluations

Expression of the target receptor (sstr2) will be determined using PET/CT imaging with the companion diagnostic imaging product ^{68}Ga-OPS202. Radiographic response and disease progression will be determined using RECIST v1.1 (CT/MRI) and PERCIST v1.0 (^{18}F-FDG-PET), tumour volume (as assessed by volumetric analysis from CT/MRI), "mGa-RECIST" for sstr2-positive lesions (CT/MRI and OPS202 PET scan) and modified PERCIST evaluating PET ^{68}Ga-OPS202 (see details in the IRC).

For each subject, the same imaging methods should be used throughout the study (e.g. ceCT or ceMRI for RECIST v1.1 tumour response assessment). Imaging parameters and approach used at screening should remain consistent throughout the study.
The same PET scanner for all the ^{68}Ga-OPS202 and scans must be used for each subject and likewise for the ^{18}F-FDG-PET (although it can be a different scanner to the ^{68}Ga-OPS202 scans).

7.1.2.1.1 Timing of Imaging Assessments

Screening

Within 3 weeks before first ^{177}Lu-OPS201 administration, each subject will undergo a ^{68}Ga-OPS202 PET/CT to evaluate eligibility for OPS201 treatment. As part of baseline assessments, a whole-body ceCT or ceMRI including brain will be performed unless a similar exam has already been performed within 28 days before first ^{177}Lu-OPS201 administration. This exam will serve as baseline assessment for RECIST v1.1 tumour response evaluation.

In addition, ^{18}F-FDG-PET will be performed as baseline assessment for PERCIST v1.0 metabolic tumour response evaluation. (A second full diagnostic CT or MRI scan is not required since one will be obtained with the ^{68}Ga-OPS202 scan, however a low dose CT will be acquired for anatomic localisation of the PET scan).

Core Treatment Phase

Imaging assessments will be performed as described in Section 5.3, the ICL and in the schedule of assessments (Table 5). Additionally, in the event of biological or clinical signs of disease progression further radiological assessments can be performed based upon the investigator's judgment.

Whole body including brain ceCT/MRI to assess tumour progression will be performed on Day 1 of each cycle (except for Cycle 1 replaced by screening scan) as well as at EOCT/EOAC visit. The scans can be performed in three images if required; head, chest, abdomen and pelvis.

^{18}F-FDG-PET will be repeated after second cycle and ^{68}Ga-OPS202 PET/CT will be repeated after second and last cycles (if different from second cycle).

Long-term Follow-up

After EOCT/EOAC visit, subjects will be followed up every 3 months to further evaluate, in addition to safety, the post-therapy efficacy (by CT or MRI) until 24 months, disease progression, administration of any other tumour-targeted therapy (e.g. chemotherapy or radiotherapy) or death, whichever occurs first (see Section 5.2.4.2).

7.1.2.1.2 Methods of Imaging Assessments

^{68}Ga-OPS202 scans are anticipated to be identified on lesions that may or may not be seen by FDG-PET scans due to the different metabolic pathways. Therefore, PERCIST, which is based on evaluating the most avid lesion, is likely to be different than one selected by ^{68}Ga-OPS202 and hence the need for evaluation by the modification (mGa-PERCIST). Likewise, RECIST requires the identification of the five largest lesions, which are generally selected by ceCT and a fused PET image. ^{68}Ga-OPS202 may provide an alternative radiological interpretation, which will be evaluated using the modification (mGa-RECIST).

Tumour Response Using RECIST v1.1

For phase I, tumour response will be evaluated using the revised RECIST guideline v1.1 (see IRC). Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-OPS201 and reached the end of Cycle 2 or EOCT visit would 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.

A modified version of RECIST ("mGa-RECIST") will also be assessed. In this second evaluation, tumours will be assessed for reading based on ^{68}Ga-OPS202 and CT. There will be a tumour mapping, so that RECIST can be determined on ^{68}Ga-OPS202 positive lesions. Since there is a possibility for a different set of lesions to be identified by ^{68}Ga-OPS202, this provides the direct response of ^{177}Lu-OPS201 on these tumours to be evaluated.

Tumour response of each subject will be graded as CR, PR, stable disease or progressive disease and unevaluable according to RECIST version 1.1. Based on this classification, the following endpoint will be calculated as defined by RECIST v1.1 and "mGa-RECIST":

- ORR: proportion of subjects with a BOR characterised as either CR or PR relative to the total number of evaluable subjects.

- DCR: proportion of subjects with a BOR characterised as CR, PR or stable disease relative to the total number of evaluable subjects.
- PFS will be evaluated as defined per RECIST version 1.1.
- Tumour response using volumetric CT/MRI assessment

The same tumours identified as target lesions and assessed by "mGa-RECIST" will also be evaluated by the percentage change in volume. The criteria are defined in the RSNA QIBA working group on tumour volume.

Tumour Response Using PERCIST v1.0

For phase I, tumour response will be evaluated using the PERCIST guideline v1.0 (see IRC). Only subjects with measurable disease at baseline, who have received at least two administrations of ^{177}Lu-OPS201 and reached EOCT visit will be considered evaluable for response.

Key elements of PERCIST include performance of PET scans in a method consistent with the NCI recommendations (UPICT) and those of The Netherlands multicentre trial group on well-calibrated and well-maintained scanners. A baseline PET scan will be obtained at approximately 1 hour (50 to 70 minutes) after ^{18}F-FDG injection. At EOCT, the PET scan will be obtained with the same interval (between ^{18}F-FDG-injection and acquisition time) reported at baseline ±15 minutes, but never less than 50 minutes from the injection. All scans will be performed on the same PET scanner with the same injected dose ±20% of radioactivity.
A PERCIST evaluation will also be performed using the ^{68}Ga-OPS202 scans (mGa-PERCIST). This will provide a different set of analyses and support the possibility of using ^{68}Ga-OPS202 as a surrogate endpoint in future studies.

Tumour metabolic response of each subject will be defined based on quantitative changes (SUL_{max} and SUL_{mean}) in tumour-to-background after two cycles versus baseline and will be graded as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD) or unevaluable according to PERCIST v1.0. The grading scale for "mGa-PERCIST" will be evaluated.

Sstr2 Targeted Tumour Uptake

Sstr2 targeted tumour uptake will be determined using PET/CT molecular imaging with the companion diagnostic imaging product ^{68}Ga-OPS202.

The change in ^{68}Ga-OPS202 PET/CT tumour uptake will be computed as a change in SUV_{max} and SUV_{mean} from baseline to EOCT/EOAC visit. These changes will also be compared to clinical outcome and ORR.

7.2 Phase II

7.2.1 Primary Efficacy Endpoint and Evaluations

The primary endpoint is ORR over the two treatment cycles of the core study. Objective response is defined using RECIST v1.1 measured by CT or MRI. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator (see Section 7.1.2.1.2). Radiological interpretation for subject management will be performed at the site, whereas efficacy evaluation will be conducted by the ICL.

7.2.2 Secondary Efficacy Endpoints and Evaluations

Secondary efficacy endpoints and evaluations are summarised in Table 10.

Table 10 Secondary Efficacy Endpoints and Evaluations in Phase II

Measure	Timepoint	Variable	Endpoint
Tumour size (longest diameter)	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Tumour response according to RECIST v1.1	BOR PFS (complemented with events of death) DRR (CR or PR lasting ≥6 months) DCR TTP TTR DoR
Tumour size (longest diameter)	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour response according to mGa-RECIST; Metabolic tumour response by ^{18}F-FDG-PET – PERCIST v1.0 and ^{68}Ga-OPS202 by mGa-PERCIST	BOR
Tumour volume	Screening[a] and 6 weeks after each ^{177}Lu-OPS201 administration (each cycle)	Mean change (%) in tumour volume assessed by volumetric CT/MRI	% change from baseline in tumour volume
Event of death	1 and 2 years	Death count	OS
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Tumour-to-background ratio by ^{18}F-FDG-PET using PERCIST v1.0	Quantitative changes in tumour-to-background ^{18}F-FDG-PET uptake
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	sstr2 targeted tumour uptake by ^{68}Ga-OPS202-PET/CT	Change in tumour uptake on ^{68}Ga-OPS202 PET/CT scan
SUL_{max} and SUL_{mean}	Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	^{68}Ga-OPS202 uptake and ^{177}Lu-OPS201 therapy response	Change in ^{68}Ga-OPS202 uptake on PET scan in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR
SUL_{max} and SUL_{mean}	Screening[a] for ^{68}Ga-OPS202 PET/CT; Screening[a] and 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)	Uptake on ^{68}Ga-OPS202 PET/CT and ^{177}Lu-OPS201 therapy response (using ceCT/MRI – RECIST v1.1)	Correlation between the uptake on ^{68}Ga-OPS202 PET/CT at baseline[a] with tumour response to ^{177}Lu-OPS201 therapy

Measure	Timepoint	Variable	Endpoint
Lesion count	For ^{68}Ga-OPS202 at screening For ^{177}Lu-OPS201 at 24 hours after first administration (Cycle 1)	Uptake on ^{68}Ga-OPS202-PET/CT and uptake on ^{177}Lu-OPS201 SPECT/CT	Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
Identification of avid lesions	Screening[a]	Number of subjects with avid lesions	Proportion of subjects with sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT

Abbreviations: ce= Contrast enhanced; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DoR=Duration of response; DRR=Durable response rate; FDG=Fluorodeoxyglucose; MRI=Magnetic resonance imaging; OS=Overall survival; PERCIST=Positron emission tomography response criteria in solid tumours; PET=Positron emission tomography; PFS=Progression free survival; PR=Partial response; RECIST=Response evaluation criteria in solid tumours; SUL=SUV normalised by lean body mass; SUV=Standardised uptake volume; TTP=Time to progression; TTR=Time to response.
[a] Screening=Baseline scan

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

Methods for assessing efficacy data in phase II are planned to be similar to those of the phase I. However, considering the phase I results these methods may be adjusted through a protocol amendment.

7.2.3.1 Patient Reported Outcomes

Patient Reported Outcomes (PROs) will be assessed in phase II using the following questionnaires: the EQ-5D-5L and EORTC QLQ-C30. The two questionnaires are commonly used, uniformly accepted and validated instruments to evaluate health outcomes in subjects with cancer. PRO questionnaires will be administered to subjects where translations into local language are available at baseline and EOCT.

7.2.3.1.1 EQ-5D-5L

The EQ-5D-5L questionnaire is a 2-page, generic preference-based Quality of Life (QoL) measure comprised of a 5-item health status measure and a visual analogue scale and is used to generate two scores. The EQ-5D utility score is based on answers to five questions to evaluate mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L visual analogue scale generates a single health status index, the analogue scale ranges from 0 to 100 in which subjects are asked to rate their current health state by drawing a line from a box marked.

7.2.3.1.2 EORTC QLQ-C30

The EORTC QLQ-C30 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumour types. It assesses 15 domains consisting of five functional domains (physical, role, emotional, cognitive, social), nine symptom domains (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and a global health status or QoL scale.

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 until at least 8 weeks after the last dose of study treatment. Information will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

The investigator will be responsible for a clinical assessment of the study participants during the whole participation of the subjects in the study, from informed consent up to discharge from the study and for the setup of a discharge plan if needed.

The sponsor medical monitor and the global patient safety physician will monitor safety data throughout the course of the study.

8.1.1 Definition of an Adverse Event

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

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.7).

Natural progression or deterioration of the 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 antitumour activity and will not be regarded as an SAE.

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related by the investigator to a relapse or an expected change or progression of the baseline malignancy.

These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or accelerated malignancy, or
- If the investigator considers the deterioration of malignancy signs and symptoms to be caused directly by the IIP/IRPP.

If there is any uncertainty about an AE being due solely to the malignancy under study, it should be reported as an AE/SAE as appropriate.

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

Adverse events will be recorded and graded according to the current version of the NCI-CTCAE version 5.0, 27 November, 2017. In view of meta-analyses and for conversion purposes, the following conversion mapping will apply if the NCI-CTCAE scale is not available for a given AE:

- NCI-CTCAE Grade 1 corresponds to mild,
- NCI-CTCAE Grade 2 corresponds to moderate,
- NCI-CTCAE Grade 3 corresponds to severe,

- NCI-CTCAE Grade 4 corresponds to life threatening/disabling,
- NCI-CTCAE Grade 5 corresponds to death (related to AE).

Where:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe**: symptoms definitely hazardous to wellbeing, significant impairment of function or incapacitation.
- **Life threatening**: any event that places the subject at immediate risk of death from the event as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death (also see Section 8.1.5).

8.1.2.2 Causality Classification

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

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

8.1.2.3 Assessment of Expectedness

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

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.

8.1.2.5 Abnormal Physical Examination Findings

Abnormal findings from physical examination that, in the judgement of the investigator, meet the definition of an AE should be recorded as such. This includes AEs of any severity, including mild, non-serious examination findings, irrespective of relation to treatment.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings (e.g. thyroid function disturbances) should be recorded as AEs. Abnormal test findings already recorded in the eCRF in specific pages (ie, abnormal ECGs) do not need to be recorded as AE unless they meet the definition of an AE (of any severity).

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 rapid 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 IRR, the investigator should promptly contact the sponsor's clinical monitor or his/her designated representative.

The signs and symptoms of IRR may include:

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

See also IRR (Section 6.3).

8.1.4 Recording and Follow up of Adverse Events

At each visit, the subject should be asked a nonleading question such as: "How have you felt since last dose?"

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

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

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

8.1.4.1 Reporting of Adverse Events

Any AE/SAE regardless of causality occurring during the study, from informed consent until 5 weeks after last study drug administration must be reported to the sponsor.

Any AE/SAE considered related by the Investigator to study treatment or study procedure that the investigator becomes aware of after completion of the End of Study (EOS)/EW visit must be reported to the sponsor and will be recorded in the clinical database and SAE form (if an SAE is reported).

8.1.5 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment group or suspected relationship to IIP/IRPP must be reported immediately (within 24 hours of the investigator's knowledge of the event) through preferably email address specified at the beginning of this protocol, filling the Ipsen SAE report form. For further details consult SAE reporting plan/clinical research organisation (CRO) agreement plan).

A SAE is any AE that:

(1) Results in death,

(2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IIP/IRPP,

(6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in 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 corporate SAEs database system.

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

Any SAE must be reported immediately (within 24 hours), using the e-mail address specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

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

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

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

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available (within 24 hours of the investigator's response). The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

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

8.1.6 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the approved IB and that the investigator identifies as related to IIP/IRPP or procedure.

8.1.7 Pregnancy

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

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor as an expedited report according to SAE reporting plan/CRO agreement plan. 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. Investigators must instruct female subjects to avoid pregnancy for at least 6 months after the end of the treatment. Due to a temporary impairment of fertility, related to a transient damage to Sertoli cells, male subjects should consider sperm banking before therapy.

The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow-up after the subject's involvement in the study has ended.

Pregnancies with a conception date before the completion of the study must also be reported to the investigator for onward reporting to the sponsor.

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

8.1.8 Deaths

For AEs leading to death, NCI CTCAE Grade 5 is the only appropriate grade (see Section 9.1.1). Deaths that cannot be attributed to an NCI CTCAE term associated with Grade 5 or that cannot be reported within an NCI CTCAE category as 'Other' have to be reported as one of these four AE options:

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

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 4.3).

If the IRPP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.5).

In all cases, the investigator must ensure the subject receives appropriate medical follow-up (see Section 8.1.4).

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

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

The sponsor must report all SUSARs to European Medicines Agency's (EMA) EudraVigilance database within 15 days. Fatal and life-threatening SUSARs should be reported immediately, with another 8 days for completion of the report.

8.2 Clinical Laboratory Tests

Blood and urine samples will be collected described in the Schedule of Assessments provided in Table 5 and Table 6 for the evaluation of haematology, serum chemistry and urinalysis.

The investigator will review the safety laboratory test results, document the review and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

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

8.2.1 Haematology

Blood samples will be collected to assess the following parameters: RBC count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and platelet count.

8.2.2 Blood Biochemistry

Blood samples will be collected to assess the following parameters:

- urea, uric acid, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate

- alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase
- albumin and total protein, total cholesterol, triglycerides, fasting glucose
- C-reactive protein (CRP)

eGFR will be calculated based on serum creatinine levels using MDRD formula.

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose. Proteinuria will be performed with dipsticks, in case of positivity, a proteinuria over 24 hours will be performed.

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

8.2.4 Pregnancy Test

A β Human chorionic gonadotrophin (HCG) serum test will be performed for all female subjects of childbearing potential at Screening (visit 1) and if clinically indicated thereafter. Moreover, a HCG urine test will be performed at Day 1 of each cycle before each ^{177}Lu-OPS201 administration. Any subject becoming pregnant during the study will be withdrawn. All subject's or subject's partner pregnancies that occur during the study treatment phase and the 2 years follow-up are to be reported as described in Section 8.1.6.

8.2.5 Other Clinical Laboratory Tests

Other clinical laboratory tests will be performed to ensure the safety of the subjects, but will not be an assessment of the safety of the study drug.

8.2.6 Hypothalamic-Pituitary-Adrenal Axis Biomarkers

Sample for hormone analysis will be collected at predose Day 1 of each Cycle and at EOCT/EOAC visit. These samples should be taken at the closest to 8.00 am and includes analysis of cortisol, TSH, parathyroid hormone (PTH), luteinising hormone (LH), follicle-stimulating hormone (FSH), free thyroxine (FT4) and IGF-1.

Hormone analyses will only be analysed in subjects who do not have substitution or therapy impacting one of the respective pituitary axis (e.g. no cortisol sampling in subjects who receive corticosteroids, no thyroid-stimulating hormone and free thyroxine sampling in subjects who have thyroxine substitution.

TSH, cortisol and IGF-1 will be measured at baseline and at end of core trial.

8.2.7 Specific Renal Safety Biomarkers

Specific exploratory renal safety biomarkers analysis will be performed on early morning midstream urine samples. The total volume of the collected urine should be documented in the eCRF.

Renal safety biomarkers include markers specific of the different renal tubule regions toxicity: GST, GSTP1, KIM-1, clusterin, cystatin-C, calbindin, beta-2 microglobulin and creatinine.

Urine samples will be collected (and frozen) at the following timepoints:

- Cycle 1:
  - Day 1: early morning, before the infusion (baseline)
  - Day 3: early morning (48 hours after the end of ^{177}Lu-OPS201 infusion at the latest)

- End of core trial Visit/Early Withdrawal Visit: early morning.

Complete instructions on processing, handling and shipping will be provided by the dedicated analytical lab in charge of the different assessments.

The results will not be communicated to the investigators.

8.2.8 Specific Pancreatic Function Biomarker

Samples for specific pancreatic function biomarker will include glycosylated haemoglobin HbA1c and glucose. Blood will be collected at Day 1 of each visit before infusion and End of core trial visit / Early Withdrawal.

8.2.9 Testicular Function Biomarkers

Samples for Testicular Function Biomarkers will include testosterone, Inhibin B and and sex hormone-binding globulin SHBG. Blood will be collected at Day 1 of each visit before infusion and End of core trial visit / Early Withdrawal.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted at the timepoints described in the Schedule of Assessments provided in Table 5 and Table 6 and height will be measured at Baseline.

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

8.4 Vital Signs

Blood pressure and heart rate will be assessed at timepoints described in the Schedule of Assessments (see Table 5 and Table 6) with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes' rest in supine position. Absolute values and change from Baseline will be analysed.

Respiratory rate and temperature will be recorded.

8.5 Electrocardiography

An ECG analysis will be included as a safety evaluation/endpoint in this study. Twelve lead-ECG and 6-hour Holter ECG will be recorded at timepoints described in the Schedule of Assessments provided in Table 5 and Table 6. For the Holter ECG, radiotransparent electrodes must be used and the Holter cables must be removed when performing imaging procedures (eg, SPECT/CT at 2 to 4 hours after the end of ^{177}Lu-OPS201 infusion).

Twelve lead ECGs will be recorded so that the different ECG intervals (RR, PR, QRS, QT, QTcF) can be measured. The ECG will be recorded with the subject in supine position after 5-minutes of rest until four regular consecutive complexes are available. Whenever possible, automated ECG interval estimates taken from the ECG recorder will be used in this study. Otherwise, ECG interval estimates will be measured manually in this study and a local ECG reader will be used.

Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS

The PK of ^{177}Lu-OPS201 and OPS201, as well as the dosimetry assessments and timepoints described below are related to the phase I of the study. PK and dosimetry assessments will also be included in phase II. However, the timepoints might be revised based on the phase I results and document as part of a protocol amendment. Time of samples collection must be accurately recorded in the eCRF.

9.1 Pharmacokinetics of ^{177}Lu-OPS201

9.1.1 Blood Sample Collection

Total radioactivity concentration in whole blood will be determined on site/locally using a gamma counter calibrated for ^{177}Lu, according to the dosimetry operational manual (DOM).

For each subject, total radioactivity concentration in whole blood will be measured. Each subject will have 20 blood samples (2 mL each) collected at Cycle 1 and Cycle 2 on the following timepoints after the end of ^{177}Lu-OPS201 infusion:

- Day 1: before the infusion (baseline), at the end of infusion (0), 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes) post infusion
- Day 2: 24±2 hours
- Day 3: 48±2 hours
- Day 4 to Day 5: 72 to 96 hours
- Day 7 to Day 8: 144 to 168 hours

Blood samples should be collected from the contralateral arm used for the study drug infusion, or from another anatomical site. Subjects with breast surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm.

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.

For subjects receiving additional administrations (up to four additional cycles), the same blood sample collection should be performed.

Complete instructions for sample collection, processing and handling will be provided in a DOM.

9.1.2 Urine Sample Collection

To determine the renal excretion of ^{177}Lu, total radioactivity concentration in urine will be determined on site/locally using a gamma counter calibrated for ^{177}Lu, according to the DOM.

The samples for urine total radioactivity concentration analysis will be taken from urine collected during four different periods at Cycle 1 only: from 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours (0 to 4 and 4 to 8 hours only in US sites) after the end of infusion, with an initial void collection shortly before the infusion (0) and a final collection, 48 hours after end of ^{177}Lu-OPS201 infusion.

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 DOM.

9.2 Nuclear Medicine Imaging for Dosimetry

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

All images will be centralised and analysed by independent readers for dosimetry analysis of the dose limiting organs and tumour lesions.

To determine the biokinetics and perform an absolute quantification, whole body scans (planar scintigraphy) and SPECT/CT will be performed at each cycle at the following timepoint ranges just after the end of ^{177}Lu-OPS201 infusion:

- Day 1: 2 to 4 hours
- Day 2: 16 to 24 hours
- Day 3: 40 to 48 hours
- Day 4 to Day 5: 72 to 96 hours
- Day 7 to Day 8: 144 to 168 hours.

At the timepoint between 16 to 24 hours, SPECT/diagnostic CT will be performed. For all other time points, SPECT/low dose CT will be performed.

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

Note that optimal schedule of the whole-body scans (planar scintigraphy) and SPECT/CT has not been established. Some adaptation of these timelines might be requiered during the study and will be decided by the dosimetry expert and the sponsor. In any case, the number of whole-body scans (planar scintigraphy) and SPECT/CT may be reduced but it will not be increased.

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.

9.3 Pharmacokinetics of OPS201

9.3.1 Blood Sample Collection

Blood will be sampled for the purpose of determining plasma levels of OPS201 using high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection, according to a separate protocol established with the dedicated analytical laboratory.

For each subject, OPS201 plasma concentration will be measured. Each subject will have 10 blood samples (2 mL each) collected at Cycle 1 only at the following time points:

- Day 1: before the infusion (baseline), at the end of infusion of ^{177}Lu-OPS201 (0), 5±1 minutes, 30±5 minutes, 1 hour (±5 minutes) and 4 hours (±30 minutes), 6 (±30 minutes), and 8 hours (±30 minutes) after the end of infusion.
- Day 2: 24±2 hours after the end of infusion of ^{177}Lu-OPS201.
- Day 3: 48±2 hours after the end of infusion of ^{177}Lu-OPS201.

Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site. Subjects with breast surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm.

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.

Note that nominal sample collection times may be changed during the study based on available data. These changes will be decided by the sponsor: the total number may be decreased but it will not be increased.
Residual plasma used for OPS201 PK analysis may also be used for exploratory analysis. This could include using leftover plasma for protein binding analysis, metabolite profiling or analysis of excipients. Plasma samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long-term stability, reproducibility).

9.3.2 Urine Sample Collection

To determine the renal excretion of OPS201, the concentration of OPS201 in urine will be determined using HPLC with MS/MS detection, according to a separate protocol established with the dedicated analytical laboratory.

The samples for urine OPS201 concentration analysis will be taken from urine collected during four different periods at Cycle 1: from 0 to 4, 4 to 8, 8 to 24 and 24 to 48 hours (0 to 4 and 4 to 8 hours only in US sites) after the start of infusion, with an initial void collection shortly before the infusion (0) and a final collection, 48 hours after the end of ^{177}Lu-OPS201 infusion.

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.

Residual urine used for OPS201 PK analysis may also be used for exploratory analysis. This could include using leftover urine for metabolite profiling or analysis of excipients. Urine samples remaining from the analysis may be retained by the sponsor for additional investigations (i.e. long-term stability, reproducibility).

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

10 EXPLORATORY BIOMARKERS AND BIOBANKING

10.1 DNA-DSB in Peripheral Lymphocytes

Blood samples will be collected at specific time points as described in the schedule of assessments in Table 5.

DNA-DSB in lymphocytes will be collected at selected sites. Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site. Subjects with breast surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm. Lymphocyte preparation will be done immediately after each blood sample collection. The accurate time of sample collection must be recorded in the eCRF. 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 by the CRO in charge of the measurement.

10.2 DNA Repair Capacity in Peripheral Lymphocytes

Blood samples will be collected at specific timepoints as described in the schedule of assessments in Table 5.

DNA repair capacity in lymphocytes will be measured using an enzymatic method in selected sites. Blood samples should be collected from the arm opposite to that of the study drug infusion, or from another site. Subjects with breast surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm. Lymphocyte preparation will be done immediately after each blood sample collection. The accurate time of sample collection must be recorded in the eCRF. 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 by the CRO in charge of the measurement.

10.3 Germinal Mutation in Blood

Blood sample will be collected in a PAXgene-DNA tube at Cycle 1 Day 1 before infusion from the arm opposite to that of the study drug infusion or from another site. Subjects with breast surgery (and in particular lymphadenectomy) should not have any blood sampling in the corresponding arm. Complete instruction for sample collection, processing and handling will be provided by the CRO in charge of the measurement.

10.4 Tumour Biopsy

Sequential biopsies will be obtained at Screening and EOCT or at disease progression, whichever occurs earlier. Baseline biopsy is mandatory and post-treatment biopsy is optional. If a historic biopsy is available and evaluable according to the requirements described below; it should not be older than 28 days prior the signature of the ICF, this biopsy can be used as baseline biopsy. The tissue material will be used for exploratory analysis to gain insight in the mechanism of action of the IRPP, the mechanism of resistance and association of sstr2 expression with the tumour uptake of ^{177}Lu-OPS201.

The biopsy size will be at least 3 to 5 mm^3. Two different tissue preparation will be done depending on the size of the collected biopsy: 1) in the case of the biopsy is smaller than 5 mm^3, the biopsy will be formalin-fixed, paraffin-embedded; 2) in case the biopsy is larger than 5 mm^3, one part will be formalin-fixed, paraffin-embedded while the extra-part will be frozen. Tumor biopsy has to be taken from the primary or metastatic lesion, whichever is accessible, ideally from a lesion which is positive for sstr2 on ^{68}Lu-OPS202 scan following eligibility

criteria and can be accomplished with reasonable safety. Tumour biopsy assessments will be performed afterwards by a CRO since they are not part of the eligibility assessment.

Tumour biopsies will be stored at the CRO during maximum 5 years after the end of the study.

Complete instructions on processing, handling and shipping will be provided by the CRO in charge of the different assessments.

10.4.1 Tumour Micro-environment and Other Markers of Interest

The biopsy will be used to evaluate tumour microenvironment and other markers of interest of the disease, such as: proliferative marker (ki-67), Tumour infiltrating immune cells (TIL/TME), DNA-DSB (gammaH2AX), target receptor evaluation (sstr2), tumour gene expression profile and gene mutations (targeted or TMB).

Specific markers depending on the indication will also be assessed in tumour biopsy (i.e. for BC: ER, progesterone receptor and HER2 protein expression and for SCLC: p53, Rb1, MYC and DLL3 gene expression).

10.4.2 DNA Repair Capacity in Tumour Tissue

DNA repair capacity will be measured in tumour tissue by a specialised laboratory in case sufficient material is available (biopsy larger than 5 mm^3). No additional biopsy will be taken for this measurement since the extra part of the biopsy described in Section 10.4.1 will only be frozen for DNA repair capacity if this biopsy is larger than 5 mm^3.

Complete instructions for biopsy, processing and handling will be provided by the CRO in charge of the measurement.

10.5 Biobanking

Analysis of biobank samples will be performed outside the scope of the main study and will be reported separately. Therefore, this analysis is optional.

For each subject who has signed a specific consent for the biobank samples, three biobanking sampling time points (see below).

Instructions for collection, processing, handling and shipment of the samples banking will be outlined in the laboratory manual.

Samples to be used for serum, cfDNA and blood for RNA, biobank storage will be taken at Day 1 (or Day -1) of Cycle 1 before infusion and at Day 1 of Cycle 2 before infusion and at EOCT/EOAC/EW.

(a) Serum: 7 mL of whole blood will be collected on specific dry tubes for serum isolation and frozen for storage

(b) Blood for RNA: 2.5 mL of whole blood will be collected in PAXgene RNA tubes.

(c) Blood for cfDNA: 10 mL of whole blood will be collected in specific tubes

Samples will be biobanked for future analysis of circulating markers, including proteins, pharmacogenetic and pharmacogenomic biomarkers and will only be collected for those subjects who have agreed to it by signing the specific informed consent form for the exploratory part of the study (see Section 14.2.1).

The biobanked samples will be stored for up to 15 years from the end of the study, to be made available for future research towards further understanding of (i) treatment response including, but not limited to, the safety profile, (ii) drug treatment mode of actions and (iii) disease understanding.

Samples will be archived in a central biorepository designated by the sponsor and according to

local administration regulations and/or the European Medicines Agency and will not carry personal identification (e.g. social security number or name). Analysis of additional biomarkers (including potential genetic research) from the biobank samples will be performed outside the scope of the main study and reported separately.

Only people designated by the sponsor will be allowed access to the samples. All information collected will be kept strictly confidential and all clinical information will be de-identified. This means that no personally identifiable information will be retained with the results of the exploratory analyses, so that no individual or collective results will be linked to the individual subject whose sample was taken in the study. No individual genetic results will be communicated to the investigator or subject unless required by local regulation.

The sponsor will comply with all local regulations related to the establishment, management and application of a human blood samples biobank.

11 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). 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)® (version 9.2 or higher).

Summary descriptive tables by treatment and over time (as applicable) will be provided.

Continuous data will be summarised with the following items: frequency, median, range, mean, standard deviation (SD) and Coefficient of Variation (CV) if relevant.

Categorical data will be presented in contingency tables with frequencies and percentages of each modality (including missing data modality). The 95% confidence interval (CI) will be calculated following the exact method.

To describe time dependent parameters (PFS, OS), Kaplan-Meier curves and life tables will be provided. The 95% CI on the median will be given.

Data from phase I and phase II will be analysed and reported separately.

An overview of the main analysis strategy is provided in the following sections.

11.1 Analyses Populations

The following population will be used during statistical analyses:

- **Eligibility screened population**: All subjects screened (i.e. who signed the informed consent).
- **Safety population**: All subjects who received at least one dose of ^{177}Lu-OPS201 or ^{68}Ga-OPS202.
  - ^{68}Ga-OPS202 safety population: All subjects who received at least one dose of ^{68}Ga-OPS202.
  - ^{177}Lu-OPS201 safety population: All subjects who received at least one dose of ^{177}Lu-OPS201.
- **MTCA evaluable population**: All subjects who received at least one dose of ^{177}Lu-OPS201 in the radioactivity escalation of the phase I of the study. The MTCA-evaluable population will be used to determine the MTCA/MTSA/MACA.
- **Intention to treat (ITT) population**: All subjects who received at least one dose of ^{177}Lu-OPS201 in the phase II of the study.
- **Per protocol (PP) population**: All subjects in the ITT population in the phase II of the study who have measurable disease at baseline, have at least one post baseline response assessment and no major protocol deviations occurred that could affect efficacy analysis. The PP population will be used for the analyses of ORR, DCR, PFS, OS, TTP, TTR and DoR.
- **Dosimetry population**: All subjects who received at least one dose of ^{177}Lu-OPS201 for whom at least one complete set of dosimetry imaging and dosimetry blood sample measurements is available. Dosimetry may be analysed separately for phase I and phase II.
- **Per protocol dosimetry population**: All subjects in the dosimetry population for whom no major protocol violations occurred affecting dosimetry variables. Dosimetry may be analysed separately for phase I and phase II.

- **Radiopharmaceutical pharmacokinetic population**: All subjects who received at least one dose of ^{177}Lu-OPS201 and have at least one measured radioactive concentration in blood. Radiopharmaceutical PK may be analysed separately for phase I and phase II.
- **OPS201 pharmacokinetic population:** All subjects who received at least one dose of ^{177}Lu-OPS201 and have no major protocol deviations affecting the PK variables and who have a sufficient number of OPS201 concentrations to estimate the main PK parameters (i.e. C_{max}, T_{max} and AUC). OPS201 PK may be analysed separately for phase I and phase II.

Subjects will be assigned to each analysis population prior to the statistical analysis.

11.1.1 Populations Analysed

For the phase I of the study, the primary analysis based on the primary safety endpoint will be performed on the MTCA evaluable population. The analysis of pharmacokinetic data will be performed on the pharmacokinetic population.

For the phase II of the study, the primary analysis based on the primary efficacy endpoint will be performed on the PP population. In addition, secondary/confirmatory analysis may be performed on the ITT population.

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

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 (ITT, PP and safety 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 interim analysis and database lock. The list may be updated, up to the point of interim analysis and database lock, to include any additional major protocol deviations impacting inclusion in the PP population.

11.2 Statistical Methodology for Phase I

11.2.1 Sample Size Determination

This is primarily a descriptive safety and tolerability study. The total number of subjects is not based on a formal statistical sample size calculation.

The actual sample size required to adequately determine the MTCA/MTSA during phase I depends on the initial activity, rate of radioactivity escalation and the observed radioactivity-toxicity and radioactivity/organ absorbed dose relationships. Simulation studies have been performed to quantify the operational characteristics (ie, precision of the MTCA/MTSA, sample size, number of subjects being over/under dosed) of the adaptive radioactivity-escalation design under a number of plausible escalation-DLT relationship scenarios. Results are provided in Appendix 1. Based on experience, the chosen sample size of 3-5 subjects per cohort is considered to be sufficient to fulfil the objectives of the study. It is anticipated that between 15 and 30 subjects will be required to establish the MTCA or MACA.

11.2.2 Significance Testing and Estimations

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

11.2.3 Statistical Methods

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

11.2.3.1 Demographic and Other Baseline Characteristics

Summary statistics will be presented for the total study population and by cohort. Frequency tables for qualitative data will be provided. Medical and surgical history findings will be summarised using MedDRA terms.

11.2.3.2 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, renal clearance) will be derived using the noncompartmental approach on the individual plasma concentration-time profiles of OPS201 and on the individual urine concentrations.

An attempt to build an integrated model taking into account PK, dosimetry as well as efficacy and safety data will be made if warranted by the data. The exploratory analysis will be captured in a separate data analysis plan and reported in a standalone report.

11.2.3.3 Radiation Dosimetry of ^{177}Lu-OPS201:

The radiation dosimetry analysis of the radiopharmaceutical ^{177}Lu-OPS201 will be performed under the responsibility of the sponsor's Clinical PK department.

Further details on dosimetry assessments and on dosimetry parameters will be provided in a separate data analysis plan.

The dosimetry assessments will be performed and reported according to the criteria set by the EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting (Lassmann 2011).

Calculations will be conducted on the following parameters (only in organs showing uptake):

- 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)

Cumulative absorbed organ doses (Gy)/Organs of highest radioactivity uptake will be identified visually. Regions of interest (ROI) will be placed over these organs to determine the relative radioactivity in the respective organs. TACs (time radioactivity curves), describing % IA/ROI of the radioactivity amount injected versus time, considering renal excretion radioactivity) will be derived. The absorbed organ doses of the dose-limiting organs (kidney, BM and liver) will be evaluated and reported to the investigator before the next administration of ^{177}Lu-OPS201 can be initiated to enable radioactivity adaptations in the event the next dose may exceed the organ limits for the kidney (23 Gy) and for the BM (1.5 Gy or up to 2 Gy during core trial and additional cycles, respectively). Of note, imaged-based dosimetry results associated to

overlying tumors/lesions resulting in absorbed dose overestimation will not be used for dose radioactivity adaptation. In this case, the dose radioactive adtaptaion will rely on an overall benefice/risk dosimetry evaluation.

A Bayesian power model will be considered to relate the cumulative ^{177}Lu-OPS201 radioactivity during Cycles 1 and 2 of the dose escalation to the cumulative absorbed dose in the BM and kidney (see details in Appendix 1). Vague priors will be used. The posterior predictive distribution of the exposure will be summarised by radioactivity level. The maximum cumulative absorbed dose where the posterior predictive probability of remaining below the target organ limits (1.5 Gy for BM and 23 Gy for kidney) will be estimated from that model, as the radiation-safety component of the MTCA.

The dosimetry for all organs other than BM and kidney will be assessed and finalised for the final clinical study report, whereas dosimetry data for BM and kidney must be available for the DRB meetings. These data can be reviewed at any time if a major safety issue occurs.

11.2.3.4 Pharmacodynamics and Efficacy Evaluation

Details for pharmacodynamic/efficacy evaluations are provided in Section 7. Tumour response will be evaluated by the ICL. Response and progression will be evaluated using the revised RECIST guideline v1.1 (see IRC), PERCIST guideline v1.0 (see IRC) as well as volumetric CT. Only subjects with measurable disease at baseline, who have received at least two administrations of study treatment and reach the end of EOCT visit will be considered evaluable for response. In addition, a mGa-RECIST and mGa-PERCIST using sstr2-positive lesions only, will be evaluated. Tumour volume and percentage change in tumour volume will be evaluated.

Efficacy data, such as best tumour response, will be summarised using descriptive statistics and will be graphically displayed if appropriate. The 95% CI will be calculated for ORR and selected secondary efficacy endpoints by treatment. Time-to-event data will be analysed by using survival methods. The results will be presented both in summary tables and graphically in Kaplan-Meier plots.

The association between pharmacodynamics parameters and selected safety, efficacy, or PK parameters may be graphically displayed. An attempt to build an integrated model taking into account PK, dosimetry as well as efficacy and safety data will be made, if warranted by the data. The exploratory analysis will be captured in a separate data analysis plan and reported in a standalone report. Further statistical analyses may be conducted. Details of the response evaluation will be given in a separate IRC. Details of the analysis will be specified in the SAP.

11.2.3.5 Safety Evaluation

For the overall study, descriptive statistics will be calculated for the safety parameters. No formal statistical analyses of safety data are planned.

Summaries will be prepared by treatment group and, as needed, by timepoint.

All AEs will be coded according to the latest version of the MedDRA and NCI-CTCAE.

Study drug treatment-emergent AE (TEAE) summaries will include the overall incidence (by system organ class (SOC) and PT), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of IIP/IRPP and SAEs.

Physical examination findings, vital signs, 12-lead ECG, ECG Holter recordings and clinical laboratory parameters will be summarised descriptively at each timepoint. Actual and change from baseline data will be calculated and summarised where data are available. The investigator's interpretation of 12-lead ECGs will be listed.

Concomitant medications will be coded using the latest version of the World Health Organisation drug dictionary (WHO-DD) and will be summarised by treatment group and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

The NCI-CTCAE version 5.0 classification will be used to classify all TEAEs and laboratory abnormalities.

Maximum grade or severity will be tabulated by subject for each MedDRA SOC and PT. Analyses of AEs and SAEs will be performed in two different ways: regardless of the relationship to the IIP/IRPP and related to the IIP/IRPP. Moreover, all AEs excluding SAEs and SAEs only will be tabulated.

For haematological and biochemical toxicities, the worst NCI-CTCAE grade 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.

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 administration of ^{177}Lu-OPS201; or
- It was present prior to receiving the first administration of ^{177}Lu-OPS201 but the intensity increased during the active phase of the study; or
- It was present prior to receiving the first administration of ^{177}Lu-OPS201, the intensity is the same but the drug relationship became related during the active phase of the study.

11.2.3.6 Maximum Tolerated Single and Cumulative Activity

Individual listings and treatment summaries of DLTs with CTCAE code and grade will be presented.

The incidence of subjects with DLTs during Cycles 1 or 2 of the radioactivity escalation will be summarised by treatment and, if possible, modelled as a function of the cumulative radioactivity for Cycles 1 and 2 using Bayesian logistic regression. The moderately-informative independent priors used during the interim analysis (see Appendix 1 for details) as well as non-informative priors will be used for this analysis in order to assess sensitivity of the estimates. Parameter estimates and model predictions will be reported with 90% credibility sets. The DLT components of the MTCA will be computed as a derived function of model parameters. If possible, the same analysis will be repeated for the Cycle 1 DLTs in order to predict the MTSA.

The posterior distribution of the MTCA and MTSA will be summarised in tabular and graphical formats.

11.2.3.7 Interim Analyses

Safety and radiation exposure data will be reviewed on an ongoing basis during the radioactivity escalation. A DRB will be set up for the radioactivity escalation decisions. For each cohort, the DRB is planned to review the safety and dosimetry data at the end of Cycle 2 of three subjects. Individual safety and organ absorbed dose data of Cycle 1 will also be reviewed at the end of Cycle 1 to determine the subject's eligibility and maintenance dose for Cycle 2.

At the time of DRB meeting, all cumulative available information will be reviewed.

Bayesian radioactivity-response and/or PK/PD modelling of DLT rates and organ absorbed dose to target organs may be performed during the planned review meetings in order to generate additional relevant information for the adaptive dose selection decisions. The DRB will review all available data and make the final decision as to radioactivity escalation, de-escalation, or

cohort expansion during the adaptive radioactivity escalation and recommended phase II dose. This group will also determine when to implement predefined stopping rules.

A specific charter will be developed to define roles and responsibilities, as well as the data set to be reviewed by the DRB.

Full analysis will be performed on the entire dataset at the EOCT/EOAC/EW and at the end of the 24-month long-term follow-up.

11.3 Statistical Methodology for Phase II

11.3.1 Sample Size Determination

The sample size is calculated using Simon's optimal two-stage design based on the ORR rate (CR + PR) following ^{177}Lu-OPS201 treatment.

For the Simon's optimal two-stage design, the hypotheses that will be tested for each cohort are: H_0: $ORR \leq ORR_0$ versus the alternative H_1: $ORR > ORR_0$ where ORR is the true objective response rate following ^{177}Lu-OPS201 treatment that warrants further clinical development, and ORR_0 is the minimum objective response rate to be excluded from further clinical development. The thresholds for ORR and ORR_0 may be updated based on results from phase I and the advances in scientific knowledge.

ORR will be analysed at the end of Stage 1 (6 weeks after the second ^{177}Lu-OPS201 administration (Cycle 2) of the core treatment period of the last evaluable subject of the Stage 1 cohort for each type of cancer). If the observed number of responders is below a predefined threshold, the respective study cohort will be stopped for futility. Otherwise, additional subjects will be treated to complete the planned enrolment. At the end of Stage 2, the null hypothesis will be rejected depending on the total observed number of responders based on a predefined threshold.

For the SCLC cohort, with 69 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 23% and an alternative hypothesis ORR rate of 40% at one-sided significance level of α=0.05. The first stage consists of 29 subjects. If seven responses or less are seen in the first 29 subjects, then the trial is stopped. Otherwise accrual continues to a total of 69 response evaluable subjects. Approximately 76 subjects are planned to be enrolled to account for 10% study dropout.

For the BC cohort, with 87 response evaluable subjects, there will be 90% power to test a null hypothesis ORR rate of 12% and an alternative hypothesis ORR rate of 25% at one-sided significance level of α=0.05. The first stage consists of 33 subjects. If four responses or less are seen in the first 33 subjects, then the trial is stopped. Otherwise accrual continues to a total of 87 response evaluable subjects. Approximately 96 subjects are planned to account for 10% study dropout.

11.3.2 Significance Testing and Estimations

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

11.3.3 Statistical/Analytical Methods

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

A SAP describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document. The SAP will be prepared before the first subject first visit.

Statistical evaluation will be performed using SAS® (version 9.2 or higher).

11.3.3.1 Demographic and Other Baseline Characteristics

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

11.3.3.2 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the ITT, PP and safety 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.

11.3.3.3 Pharmacokinetic Data

The pharmacokinetic data analysis, if collected in phase II, will be performed independently by a CRO under the supervision of the sponsor's Clinical PK department as described in Section 9.3.

Individual listings and summary tables of OPS201 plasma concentrations and amount excreted in urine will be provided.

11.3.3.4 Efficacy Evaluation

At the end of phase II, descriptive summaries will be provided for all primary and secondary efficacy endpoints. For the primary endpoint, final analysis will take into account the sequential sampling procedure of the design and the underlying binomial distribution assumed by the Simon's optimal two-stage design.

As indicated in Section 7.2.1, the primary efficacy variable is the ORR over the two treatment cycles of the core study measured by CT or MRI using RECIST version 1.1. ORR is defined as the percentage of subjects who have achieved a response of CR or PR. Exact 95% CIs based on the binomial distribution will be reported. Tumour response assessments are performed 6 weeks after each administration of ^{177}Lu-OPS201 during the core study or at the time of occurrence of first clinical signs of disease progression as determined by the investigator.

As indicated in Section 7.2.2, the secondary efficacy variables are the below listed variables measured after administration of study treatment:

- DRR, defined as the percentage of subjects who have achieved a response of CR or PR lasting more than 6 months.
- PFS as determined from start of study treatment until occurrence of event. PFS is defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of first documented disease progression as determined by the investigator or death due to any cause, whichever occurs first. Rules for declaring PFS events versus censors will be described in the SAP.
- OS is defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of death due to any cause.
  - One-year and two-year survival are defined as the subject survival probability at 1 year and 2 years, respectively, after the date of first dose of ^{177}Lu-OPS201.
- Other response endpoints as per RECIST version 1.1:

- disease control rate (DCR), defined as the percentage of subjects who have achieved a response of CR, PR or stable disease.
- TTP, defined as the time from date of first dose of ^{177}Lu-OPS201 to the date of first documentation disease progression as determined by the investigator.
- TTR, defined as the time from the date of first dose of ^{177}Lu-OPS201 to the date of the first documentation of a response (CR or PR whichever occurs first) in a subject who responded.
- duration of response (DoR), defined as the time from date of first documentation of response (CR or PR whichever occurs first) to the date of disease progression or to death due to any cause, whichever occurs first.

Time-to-event parameters will be graphically displayed using Kaplan-Meier estimates. Median event times and 2-sided 95% CIs will be reported on the graphs. Two-sided 95% CIs may be displayed for some other parameters.

- Mean change (%) in tumour volume at 6 weeks after each ^{177}Lu-OPS201 administration compared to baseline, as assessed by volumetric CT.
- Correlation between tumour uptake on ^{68}Ga-OPS202 PET/CT (assessed based on SUV_{max} and SUV_{mean}) at screening with tumour response to ^{177}Lu-OPS201 therapy from Screening to 6 weeks after second ^{177}Lu-OPS201 administration (second cycle)
- Correlation between the uptake of ^{68}Ga-OPS202 in tumour lesions expressing sstr2 on PET/CT images and the uptake on ^{177}Lu-OPS201 SPECT/CT
- Change in ^{68}Ga-OPS202 uptake on PET scan after the second ^{177}Lu-OPS201 administration (second cycle) as assessed by SUV_{max} and SUV_{mean} in subjects screened for ^{177}Lu-OPS201 treatment as compared to clinical response and ORR.
- Proportion subjects with of sstr2-positive tumour lesions by ^{68}Ga-OPS202 PET/CT scans as assessed by the identification of avid lesions in subjects screened for ^{177}Lu-OPS201 treatment at baseline.

Subject Reported Outcomes (only Phase II)

- Changes in health-related quality of life scores from baseline to EOCT measured by EQ-5D-5L and EORTC QLQ-C30.

Exploratory endpoints

- The association between the uptake on ^{68}Ga-OPS202 PET/CT with sstr2 expression on tumours as determined by IHC.
- Change in renal safety biomarkers compared to baseline.
- Change from baseline in tumour microenvironment, transcriptomics, DNA repair, gene mutations and other disease markers of interest.
- Change from baseline in DNA repair capacity in blood.

11.3.3.5 Adjustment for Country/Centre Effect

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

11.3.3.6 Safety Evaluation

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

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

Concomitant medication will be coded by using WHO-DD (latest available version) and will be summarised.

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs, blood pressure, heart rate, ECG parameters, clinical laboratory tests etc. at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Clinically significant ECG findings will also be flagged. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

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

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

11.3.4 Subgroup Analyses

Not applicable.

11.3.5 Interim / Futility Analyses and ISAC Safety Review Committees

Phase II

An interim analysis will be performed for futility based on the first stage of Simon's optimal two-stage design within each cohort.

For the SCLC cohort, the first stage consists of 29 subjects. An analysis will be conducted after approximately 29 subjects have been assessed on the ORR. The ORR assessment cut-point for the 29th subject is 6 weeks after Cycle 2 dose. The probability of early termination (PET) after the first stage is 0.6555.

For the BC cohort, the first stage consists of 33 subjects. An analysis will be conducted after approximately 33 subjects have been assessed on the ORR. The ORR assessment cut-point for the 33rd subject is 6 weeks after Cycle 2 dose. The probability of early termination (PET) after the first stage is 0.6374.

The details of the interim analysis will be described in the SAP.

An ISAC will be established to monitor the safety and progress of the study on a regular basis. The committee will operate independently from the sponsor and the clinical investigators. To minimise the potential introduction of bias, these individuals will not have any direct contact with the study site personnel or subjects. ISAC members will be selected for their expertise in oncology.

The ISAC will be responsible for any adhoc assessments of safety and futility for each phase II cohort, and can meet as needed to recommend protocol modifications, or any other actions including but not limited to:

- Changing the eligibility criteria if the risks of the intervention seem to be higher in a subgroup;

- Altering the drug product dosage and/or schedule if the AEs observed appear likely to be reduced by such changes;
- Identifying information needed to inform current and future trial subjects of newly identified risks via changes in the consent form and, in some cases, obtaining reconsent of current subjects to continued trial participation.

Further details regarding the ISAC and their requirements will be outlined in the ISAC charter.

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.

Sponsor-delegated Clinical Research Associates will have access to source data and documents for source data verification purposes during monitoring visits.

Auditors, study monitors 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, radiology department).

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

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:

- ***Non-substantial 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:

(1) The deviation has harmed or posed a significant or substantive risk of harm to the research subject.

(2) The deviation compromises the scientific integrity of the data collected for the study.

(3) The deviation is a wilful or knowing breach of human subject protection regulations, policies, or procedures on the part of the investigator(s).

(4) The deviation involves a serious or continuing noncompliance with any applicable human subject protection regulations, policies, or procedures.

(5) 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, they must immediately inform the sponsor.

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 CRF 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

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

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

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

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

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

A DRB will review data for the phase I of the study (refer to Section 3.1.4.1.4).
An Operations Committee will be composed of investigator and sponsor representatives and, as appropriate, of representatives of a dedicated study specific management organisation to

efficacy and safety data at each interim analysis for the phase II. A specific charter may be developed to define roles and responsibilities.

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

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

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 (Section 1.8).

FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

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

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

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

14.2 Informed Consent for Participation in the Study

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

This study has the option for subjects to consent to the collection of samples for biobanking for future exploratory analysis 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 ethics committee(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 assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

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

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Recording of Study Data

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

The investigator must record all data relating to protocol procedures, IIP/IRPP administration, laboratory data, safety data and efficacy ratings on the CRFs/eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete CRFs/eCRFs to appropriately qualified staff having certified user access to the eCRF. Subject completed diaries and questionnaires will be printed and entered by the site personnel into the eCRF.

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

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

15.2 Data Management

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

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigator site, (for further details please see Section 13.3 Monitoring Procedures).

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

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

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

The coding of an AE, medical history, surgical procedures and concomitant medication terms will be performed by a CRO and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

Only data from subjects who signed the trial informed consent form will be reported in the eCRFs and collected in the sponsor's database.

For screen failure subjects, at minimum the Unique Subject Identifier, the date of informed consent signature, the information that the subject failed screening and the potential AEs which occurred during the screening phase will be reported in the eCRFs and collected in the sponsor's database.

15.3 Record Archiving and Retention

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

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

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

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.

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

16.2 Insurance, Indemnity and Compensation

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

17 REPORTING AND PUBLICATIONS OF RESULTS

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. 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.

17.2 Clinical Study Report

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

An analysis will be performed on the final response data after the last subject has completed the treatment period. This analysis will be included in an interim study report/s. An addendum to the CSR will include the analysis of data from the follow-up period and will be prepared after the last subject completes the follow-up period.

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

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