PROTOCOL TITLE: A NON-RANDOMISED PHASE II STUDY TO EVALUATE THE OPTIMAL UPTAKE TIME OF ^{68}GA-OPS202 AS A SSTR2 POSITIVE PET IMAGING AGENT IN SUBJECTS WITH NEWLY DIAGNOSED BREAST CANCER
(Sub-study of Master Protocol Ipsen 001 Version 1.0: 02 February 2018)

STUDY PROTOCOL
STUDY number: D-FR-01070-003
^{68}Ga-OPS202
EudraCT number: 2018-000028-33/NCT Number: XXXX
Version 4.0, Amendment 3.0: 20 May 2019

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Persons supplied with this information must understand that it is strictly confidential. Information contained herein cannot be disclosed, submitted for publication or used for any purpose other than that contemplated herein without the sponsor's prior written authorisation.

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01070-003 entitled: A non-randomised phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer. 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.

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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol D-FR-01070-003 entitled A non-randomised, phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

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SUMMARY OF CHANGES

The current version of the protocol was released on 20 May 2019 and includes Amendment 3. For all protocol amendments, amendment forms were prepared and are provided in the Appendices listed in Table 1. All modifications (except minor changes) are presented in the appendices.

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	27 June 2018	Appendix 1
2	14 September 2018	Appendix 2
3	20 May 2019	Appendix 3

SYNOPSIS

Name of sponsor/company: IPSEN.

Name of finished product: ^{68}Ga-OPS202 - ^{68}Ga-satoreotide trizoxetan

Name of active ingredient(s): ^{68}Ga-OPS202 - INN for OPS202 is satoreotide trizoxetan

Title of study: A non-randomised, phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer.

Study number: D-FR-01070-003

The cohort investigated in this study is part of Master Protocol Ipsen 001 Version 1.0 encompassing specific sub-studies to evaluate ^{68}Ga-OPS202 as a positron emission tomography (PET) imaging product in different types of somatostatin receptor 2 (sstr2)-positive tumours.

Number of planned centres: Estimated two specialised centres in Europe

Planned study period: FPI: July 2018 - LPO: December 2019	**Phase of development**: Phase II.

Study type: non-randomised phase II

Objectives:

Primary study objective:

The co-primary objectives of the study are:

- To evaluate the percentage of women with newly diagnosed breast cancer who have sstr2 positive lesions that are identified using ^{68}Ga-OPS202
- To define the optimal PET imaging time of ^{68}Ga-OPS202 at 0.5, 1.0 and 2 hours post injection, based on detected lesions in adult women with sstr2 positive newly diagnosed early or advanced breast cancer.

Secondary study objectives:

- To further define the optimal uptake time of ^{68}Ga-OPS202 based on quantitative maximum standardised uptake value (SUV_{max}) and other quality parameters
- To describe the safety and tolerability of ^{68}Ga-OPS202 in women with newly diagnosed (early or advanced) sstr2 positive breast cancer.

Exploratory objectives:

- To provide preliminary estimates of the sensitivity of ^{68}Ga-OPS202 PET/computed tomography (CT) scan imaging, as well as SUV ratio (SUV_{max} lesion / SUV_{mean} reference tissue) and signal-to-noise ratios (SNR)
- To assess the correlation in terms of number of avid lesions between ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET and ^{68}Ga-OPS202
- To assess the correlation between ^{68}Ga-OPS202 tumour uptake with results from immunohistochemistry staining of sstr2.

Study hypothesis: The uptake of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.

Methodology:

Study design:

This is a non-randomised phase II study, with an approximately 4-week duration for each subject and central review-blinded reader endpoint.

All subjects will receive a single dose of ^{68}Ga-OPS202 (Investigational Imaging Product; IIP), consisting of a peptide mass up to 45 µg, with a radioactivity range of 150-200 MBq. ^{68}Ga-OPS202 is prepared up to 3 hours prior to administration by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit.

Three PET acquisitions will be performed at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection. ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards.

A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Thus, only one ceCT scan is required to minimise radiation dose. Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained.

All images (^{68}Ga-OPS202 PET/CT scans, ^{18}F-FDG-PET scan, and ceCT scan) will be sent to an imaging core laboratory (ICL) for central blinded reading.

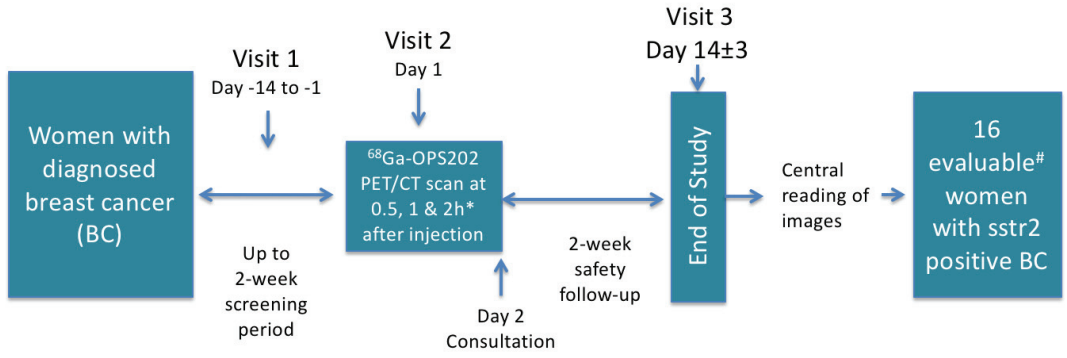
All decisions regarding subjects' medical management will be made locally by the treating physicians (images read locally for this purpose). The ICL/central readers will only evaluate the images for the study endpoints and the information will not be provided to the sites on an individual subject basis.

Duration of participation for a subject:

Subject participation in the study is estimated to last approximately 4 weeks and will include:

- Visit 1: within a screening period of up to 14 days prior to the ^{68}Ga-OPS202 administration
- Visit 2 (Day 1): a single intravenous (i.v.) injection of a fixed activity range of ^{68}Ga-OPS202 followed by PET acquisitions at 0.5, 1 and 2 hours ±10 minutes post dosing (see Methodology Section above)
- Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety.
  Within the study an ^{18}F-FDG-PET scan and also a ceCT scan must also be acquired.

Figure S1. Study Design



*A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). 18F-FDG-PET scan, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards
Women with readable ceCT scan and at least two ^{68}Ga-OPS202 PET scans that are readable

CT=computed tomography, h=hour, IIP=investigational imaging product, PET=positron emission tomography
Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 positive evaluable subject scans.

Assessments:

The Screening Visit (Visit 1) will be performed within 14 days prior to the first ^{68}Ga-OPS202 administration. At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination and vital signs, laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available. Tumour biopsy blocks or slides are required for the evaluation of sstr2 expression by immunohistochemistry staining with the anatomical location of the lesion(s) indicated to be matched with the ^{68}Ga-OPS202 PET/CT images.

Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET imaging at 0.5, 1 and 2 hours after the injection of the IIP. An ^{18}F-FDG-PET scan will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards. If the ^{18}F-FDG-PET scan is performed before the informed consent signature, subject approval is required for using this image set.

A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired with PET scans when necessary for attenuation correction.

Subjects may be hospitalised overnight upon completion of ^{68}Ga-OPS202 PET/CT scans at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for a physical examination and laboratory tests.

An End of Study Visit (Visit 3) will take place on Day 14 (±3 days), during which the investigator will collect the safety information required by the study protocol. At the end of Visit 3, the subject's participation in the study will end. For any adverse event (AE) emerging or worsening during the study that persists beyond Visit 3, the investigator will monitor the subject until the AE is resolved or considered stabilised.

Independent read of PET/CT images:

This is a non-randomised 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 acquisition time of the PET scans and CT scans, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical exam findings.

The 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. Two readers will read 100% of all the images and third will adjudicate any differences.

Number of subjects planned:

Considering the estimated prevalence of sstr2 overexpression in breast cancer, it is anticipated that a total of approximately 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 PET/CT imaging, to obtain 16 sstr2 positive breast cancer (BC) evaluable subjects. However, when the ICL identifies 16 sstr2 positive evaluable subject scans, with a minimum of two subjects with advanced disease, the study will be complete.

Futility Stopping Rules

If less than three sstr2 positive evaluable subject scans out of 30 consecutive subjects screened with ^{68}Ga-OPS202 PET/CT, or less than 8 out of 50, the study will be stopped.

The Sponsor may consider stopping subject recruitment and revisit the study design with possible termination of the study when justified.

Diagnosis and criteria for inclusion:

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

Inclusion criteria:

1. Women aged 18 years or older
2. Subjects with newly diagnosed (early or advanced) breast cancer
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤2
4. Adequate bone marrow, liver and renal function, with:
   - Calculated glomerular filtration rate (GFR): ≥45 mL/min
   - Albumin: >30 g/L
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP): ≤ 5 times upper limit of normal (ULN)
   - Bilirubin: ≤3xULN (3x1.1 mg/dL)
   - Leukocytes: ≥3x10^9/L, and neutrophils: ≥ 1x10^9/L
   - Erythrocytes: ≥3.5x10^{12}/L
   - Platelets: ≥90x10^9/L
5. Signed written informed consent prior to any study-related procedures.

Exclusion criteria:

1. Subjects with resected primary tumour
2. Subjects with confirmed ductal carcinoma in situ
3. Men with breast cancer

4. Presence of an active infection at screening or history of a serious infection within the previous 6 weeks prior to the first ^{68}Ga-OPS202 administration that might interfere with the PET and/or CT analysis
5. Subjects who have received any therapy for breast cancer
6. Prior or planned administration of a radiopharmaceutical within 8 half-lives of the radionuclide
7. Clinically relevant trauma within 2 weeks prior to first ^{68}Ga-OPS202 administration
8. Any condition that precludes the proper performance of PET and/or CT scan:
   - Subjects who are not able to tolerate the CT contrast agent
   - Subjects with metal implants or arthroplasty, or any other objects that might interfere with the PET and/or CT analysis
   - Subjects unable to raise arms for prolonged imaging purposes
   - Subjects unable to lie still for the entire imaging time
   - Subjects weighing greater than 110 kg (243 lb)
9. Known hypersensitivity to radiolabelled NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid), to Gallium-68, to somatostatin analogue peptide JR11 or to any of the excipients of ^{68}Ga-OPS202
10. History of, or current active allergic or autoimmune disease, including asthma or any condition requiring long-term use of systemic corticosteroids
11. Known human immunodeficiency virus (HIV) or positive serology for HIV, hepatitis B or C
12. Administration of another investigational medicinal product within 30 days prior to first ^{68}Ga-OPS202 administration
13. Subjects who are pregnant, breast feeding or of childbearing potential not willing to practice effective contraceptive techniques during the study treatment period and for 30 days after the last dose of ^{68}Ga-OPS202 administration; pregnancy test must be performed at the start of the study and prior to ^{68}Ga-OPS202 administration
14. Subjects who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study, including any mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude
15. Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus, and/or subjects treated with curative intent and free from disease for more than 5 years).

Test product, dose, mode of administration:

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

- JR11, an antagonist somatostatin analogue that binds to sstr2 receptors
- NODAGA, a chemical chelator moiety, and
- ^{68}Ga, a positron emitter radionuclide, with a half-life of 68 minutes.

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 50 µg lyophilised OPS202 and excipients and a second containing a solution for

reconstitution. After 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 dose at the time of administration, taking into account the decay of ^{68}Ga. All subjects will receive a single dose of IIP, with ^{68}Ga radioactivity dose of 150-200 MBq, as a slow i.v. bolus injected over 1 minute.

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

Duration of treatment: ^{68}Ga-OPS202 will be administered as a slow i.v. bolus injected over 1 minute once at Baseline/Day 1 (Visit 2).

Reference therapy, dose and mode of administration:

Comparator compound/placebo:

In this study, there is no comparison with a reference-imaging product. The primary statistical analyses will evaluate the differences (if any) between the three different scan acquisition timepoints of the ^{68}Ga-OPS202 PET.

Other treatments: Any medication and/or therapy taken or received by the subject during the study, other than the study IIP (^{68}Ga-OPS202), will be considered concomitant medication whether or not it is targeting the studied breast tumour. Concomitant treatments are to be prescribed, modified, or discontinued at the investigator's discretion. Subjects must be withdrawn from the study, but followed-up when possible for further data collection, if at least one of the protocol-prohibited medications/therapies (see above-mentioned eligibility criteria) is received by the subjects during the study period up to the end of the ^{68}Ga-OPS202 PET/CT scan at Visit 2.

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

Criteria for evaluation (endpoints):

Efficacy:

The primary and secondary imaging endpoints will be read by third-party independent readers. Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain.

Co-primary efficacy endpoints and evaluation

- Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than the non-tumoural liver and lung parenchyma).
- Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in the primary breast lesions.

Secondary endpoints and evaluations

Key secondary endpoint:

- Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of

the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.

- The SUV_{mean} and SUV_{max} in the primary lesion between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain); the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.

Other secondary endpoints:

- Differences in relative lesion counts as a ratio of the number of lesions detected by ^{68}Ga-OPS202 at 0.5, 1 and 2 hours post dose respectively, compared to the number of lesions assessed by standard-of-truth (descriptive analyses). The standard-of-truth is the ^{18}F-FDG-PET scan images acquired at any time during the study period (including the Screening period). This will be calculated by (number of lesions detected by ^{68}Ga-OPS202) / (number of lesions detected by ^{18}F-FDG-PET).
- Differences of absolute number of lesions between the three PET acquisition timepoints detected in each of the following anatomic sites:
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
  - Brain

The second co-primary and appropriate secondary endpoints will also be evaluated on a MBq/kg of body weight.

The secondary endpoints will be summarised by each of the three PET acquisition timepoints (0.5, 1 and 2 hours).

Exploratory endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of breast cancer expressing sstr2 positive by both subject-based and lesion-based analysis compared to standard-of-truth
- SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} at the three PET acquisition timepoints.
- Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG-PET.
- Estimated correlation between ^{68}Ga-OPS202 PET uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

Further details on efficacy endpoints are described in the Imaging Review Charter (IRC).

Statistical methods:

Method of randomisation:

There is no randomisation in the design of the present study. However, the image presentation to the central readers will be performed in a blinded manner; thus, the readers will be blinded to the image sequence.

Sample size and power considerations:

It is anticipated that a total of approximately 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 PET/CT imaging, to obtain around 16 sstr2 positive BC evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be screened with ^{68}Ga-OPS202 in the study will be over 50. However, when the ICL identifies 16 sstr2 positive evaluable subjects, with a minimum of two subjects with advanced disease, the study will be complete.

This estimation of 16 sstr2 positive BC evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited to ensure an adequate sample size in the sstr2 positive BC evaluable set.

Statistical analysis:

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

The primary endpoint and secondary tumour-to-background ratio and SUV_{max} endpoints' analyses will be performed.

Overall differences among the three acquisition timepoints will be analysed.

Interim analysis:

No interim analysis is planned for this study.

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LIST OF ABBREVIATIONS

ABBREVIATION	Wording Definition
βHCG	Beta human chorionic gonadotropin
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BC	Breast cancer
bpm	Beats per minute
BUN	Blood urea nitrogen
CA	Competent Authorities
CFR	Code of Federal Regulations (United States of America)
CRF	Case report form
CRO	Contract research organisation
CT	Computed tomography
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fluorodeoxyglucose
GCP	Good Clinical Practice
GEP-NETs	Gastroenteropancreatic neuroendocrine tumours
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
%IA/g	Percentage injected activity per gram of tissue
ICH	International Conference on Harmonisation
ICL	Imaging core laboratory
IEC	Independent ethics committee
IIP	Investigational imaging product

ABBREVIATION	Wording Definition
INN	International nonproprietary name
IND	Investigational New Drug
IRB	Institutional review board
IRC	Imaging review charter
i.v.	Intravenous
LDH	Lactate dehydrogenase
max	Maximum
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
MTD	Maximum Tolerated Dose (Dosage)
NA	Not applicable
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NET	Neuroendocrine tumour
NOAEL	No observable adverse effect level
NOS	Not otherwise specified
PP	Per protocol
PET	Positron emission tomography
PT	Preferred term
RBC	Red blood cell(s)
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SDV	Source document verification
SE	Standard Error
SmPC	Summary of Product Characteristics
SNR	Signal-to-noise ratio
SOP	Standard Operating Procedure
SPECT	Single-photon emission computed tomography
sstr	Somatostatin receptor
sstr2	Somatostatin receptor subtype 2

ABBREVIATION	Wording Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV_{max}	Maximum standardised uptake value
SUV_{mean}	Mean standardised uptake value
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal range
US(A)	United States (of America)
WBC	White blood cell(s)
WHO	World Health Organisation
WHO-DD	World Health Organization (WHO) drug dictionary

1 BACKGROUND INFORMATION

1.1 Introduction

Somatostatin-based radiolabelled agonistic peptides have been successfully introduced into the clinic for targeted imaging of somatostatin receptor (sstr)-positive neuroendocrine tumours (NETs), especially of the clinically most relevant subtype sstr2. Currently, three somatostatin-based radiolabelled peptide analogues are approved in the United States and/or Europe: namely, ^{111}In pentetreotide (Octreoscan™), which is based on gamma rays, visualizing sstr-positive tumours in whole body single-photon emission computed tomography (SPECT) [1], ^{68}Ga-DOTA-TATE (NETSPOT®), and ^{68}Ga-DOTA-TOC (Somakit TOC) used with positron emission tomography (PET) imaging that provides several advantages over SPECT such as temporal and spatial resolution, reduced radiation burden and diminished examination time [2, 3].

1.2 Name and Description of Investigational Imaging Product

OPS202 (satoreotide trizoxetan) is a new generation somatostatin analogue (antagonist) compound with potential superior tumour detection as a consequence of the availability of more binding sites for both active and inactive sstr2. It consists of the small somatostatin analogue JR11 conjugated to the strong cyclical 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) to produce ^{68}Ga-OPS202. This complex (^{68}Ga-OPS202) is being developed as a PET imaging agent for the detection of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in patients.

^{68}Ga is a short-lived (half-life: 68 min) positron-emitting isotope generated from decay of the parent isotope germanium-68 (^{68}Ge, half-life: 271 days). In the clinic (radiopharmacy), it can be derived from a ^{68}Ge/^{68}Ga-generator. One of the main advantages of ^{68}Ga is its cyclotron-independent availability, providing an inexpensive, decentralised and convenient alternative to cyclotron-generated isotopes. Further key radiochemical characteristics of ^{68}Ga are summarised in Table 2.

Table 2 Radiochemical Characteristics of ^{68}Ga

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

^{68}Ga-OPS202 is being developed as a PET diagnostic imaging agent for sstr2 positive tumours. A more detailed description of the product is given in Section 3.4.

1.3 Findings from Nonclinical and Clinical Studies

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

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

Two anecdotal reported cases under compassionate use at the Zentralklinik Bad Berka provided preliminary data supporting the safety and efficacy of ^{68}Ga-OPS202. These two subjects with a diagnosis of NETs were imaged with radiolabelled sstr2 antagonist ^{68}Ga-OPS202, which was compared to ^{68}Ga-DOTA-TOC imaging. In the first subject, significantly higher uptake with ^{68}Ga-OPS202 compared to ^{68}Ga-DOTA-TOC was detected in the large primary pancreatic tumour (maximum standardised uptake value (SUV_{max}) of 21% or higher) and additionally two osseous metastases were detected which were not seen in the ^{68}Ga-DOTA-TOC PET/CT examination in this subject. In the second subject, three more liver metastases were detected by ^{68}Ga-OPS202 compared to detection by ^{68}Ga-DOTA-TOC. This may have been due to the favourably higher tumour-to-liver uptake ratio with ^{68}Ga-OPS202 imaging when compared to the ^{68}Ga-DOTA-TOC evaluation. These imaging results encouraged further investigation of ^{68}Ga-OPS202 being a promising radiopharmaceutical tracer and potentially superior to the standard Octreoscan™ or the newly approved ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-TOC in the diagnosis of GEP-NET lesions.

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

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

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

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

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

1.4 Selection of Investigational Imaging Product and Dosages

In an on-going study in subjects with NETs (Study D-FR-01070-002), two target peptide mass dose ranges (5-20 µg and 30-45 µg) and three radioactivity dose ranges are being investigated:

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

The present study will add information on the optimal PET/CT acquisition time using the highest radioactivity range. Although there is over-expression of sstr2 in many breast cancer tumours, this level is lower than seen in subjects with NETs. Therefore, it is anticipated that in order to obtain optimal images with ^{68}Ga-OPS202 in non-NETs subjects, the highest injected radioactivity dose range would be appropriate.

A more detailed description of administration procedures is given in Section 6.1.

1.5 Compliance Statement

The study will be conducted in compliance with independent ethics committees (IECs), 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.

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 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 that they comply with GCP requirements. The IEC approval must identify the protocol version as well as the documents reviewed.

1.6 Population to Be Studied

Several types of tumours other than NETs express sstr2 making the imaging of these tumours with peptide receptor radionuclide such as ^{68}Ga-OPS202 possible. This study will enrol adult female subjects with newly diagnosed early or advanced breast cancer to detect those expressing sstr2.

To identify the evaluable subjects for the analysis of the primary endpoint, tumours/metastases expressing sstr2 will be identified and documented through the lesion uptake of the diagnostic compound (^{68}Ga-OPS202). Only subjects showing tumour ^{68}Ga-OPS202 uptake (avid lesion) in target tissues (primary tumour, lymph nodes and/or metastases) higher than non-tumoural liver parenchyma by PET imaging will be selected for the comparison of images at different acquisition timepoints.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

^{68}Ga-OPS202 PET/CT has been solely investigated in patients with NETs. Non-NETs expressing sstr2 may have a different level of receptors expression raising the question of a possible difference in terms of optimal uptake time. This phase II study aims to estimate firstly the percentage of female subjects with newly diagnosed breast cancer who have sstr2 positive lesions using ^{68}Ga-OPS202, secondly in those subjects with sstr2 positive tumours, the optimal PET acquisition time based on detected number of lesions and tumour to background ratio in subjects with sstr2 positive breast cancer. The study will also expand the evaluation of ^{68}Ga-OPS202 safety in patients with non-NETs expressing sstr2.

2.2 Study Objectives

The co-primary objectives of the study are:

- To evaluate the percentage of women with newly diagnosed breast cancer who have sstr2 positive lesions that are identified using ^{68}Ga-OPS202
- To define the optimal PET imaging time of ^{68}Ga-OPS202 at 0.5, 1.0 and 2 hours post injection, based on detected lesions in adult women with sstr2 positive newly diagnosed early or advanced breast cancer.

The secondary objectives of the study are as follows:

- To further define the optimal uptake time of ^{68}Ga-OPS202 based on quantitative SUV_{max} and other quality parameters
- To describe the safety and tolerability of ^{68}Ga-OPS202 in women with newly diagnosed (early or advanced) sstr2 positive breast cancer

The exploratory objectives of the study are as follows:

- To provide preliminary estimates of the sensitivity of ^{68}Ga-OPS202 PET/CT scan imaging, as well as SUV ratio (SUV_{max} lesion/SUV_{mean} reference tissue) and signal-to-noise ratios (SNR)
- To assess the correlation in terms of number of avid lesions between ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET and ^{68}Ga-OPS202
- To assess the correlation between ^{68}Ga-OPS202 tumour uptake with results from immunohistochemistry staining of sstr2.

2.3 Study Hypothesis

The uptake of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.

3 STUDY DESIGN

3.1 General Design and Study Schema

This is a non-randomised phase II study, with an approximately 4-week duration for each subject and central review-blinded reader endpoint.

All subjects will receive a single dose of ^{68}Ga-OPS202 (IIP), consisting of a peptide mass up to 45 µg, with a radioactivity range of 150-200 MBq. ^{68}Ga-OPS202 is prepared up to 3 hours prior to administration by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit.

Three PET images will be acquired at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection.

^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards.

A single ceCT scan is required for the study. This can be acquired following either of the two PET scans (FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Only one ceCT scan is required to minimise radiation dose. Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained. For the ^{68}Ga-OPS202 PET scan a single low dose CT scan is preferred for the 0.5 and 1.0-hour post dosing acquisitions.

All images (^{68}Ga-OPS202 PET/CT scans, ^{18}F-FDG-PET/CT scan, and ceCT scan) will be sent to an imaging core laboratory (ICL) for central blinded reading. See Section 7 and the Imaging Review Charter (IRC) for further details.

All decisions regarding subjects' medical management will be made locally by the treating physicians (images read locally for this purpose). The ICL/central readers will only evaluate the images for the study endpoints and the information will not be provided to the sites on an individual subject basis.

The Screening Visit (Visit 1) will be performed within 14 days prior to the ^{68}Ga-OPS202 administration. At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination and vital signs, laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available. Tumour biopsy, which is not a prerequisite for inclusion, is routinely performed for confirmation and staging of the disease, as well as classification according to hormone receptor status and human epidermal growth factor receptor 2 (HER2) status. For the study, the collection of an archived tumour sample (a block is preferred over paraffin embedded slides) is required for the evaluation of sstr2 expression by immunohistochemistry staining.

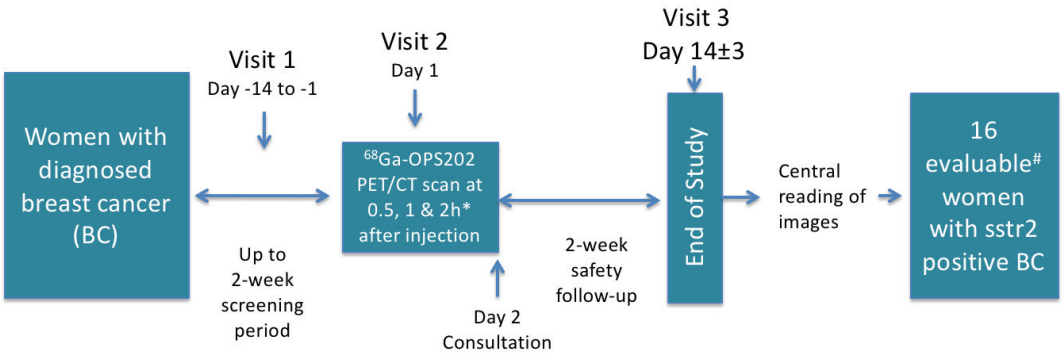
Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET acquisition at 0.5, 1 and 2 hours after the injection of the IIP. A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired with PET scans when necessary for attenuation correction.

Subjects may be hospitalised overnight upon completion of the ^{68}Ga-OPS202 PET/CT scans at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for vital signs and laboratory tests. Also an ^{18}F-FDG-PET scan and ceCT scan will be arranged if not already acquired.

An End of Study Visit (Visit 3) will take place on Day 14 (±3 days), during which the investigator will collect the safety information required by the study protocol (see Criteria of safety evaluation below). At the end of Visit 3, the subject's participation in the study will end. For any adverse event (AE) emerging or worsening during the study that persists beyond Visit 3, the investigator will monitor the subject until the AE is resolved or considered stabilised.

Study design scheme is presented in Figure 1.

Figure 1 Study Design



*A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). 18F-FDG-PET scan, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards

Women with readable ceCT scan and at least two ^{68}Ga-OPS202 PET scans that are readable

CT=computed tomography, h=hour, IIP=investigational imaging product, PET=positron emission tomography

Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 positive evaluable subject scans.

3.2 Primary and Secondary Endpoints and Evaluations

The primary and secondary imaging endpoints will be read by third-party independent readers. Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain.

3.2.1 Primary Efficacy Endpoint and Evaluation

- Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than the non-tumoural liver and lung parenchyma).
- Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in the primary breast lesions.

3.2.2 Secondary Endpoints and Evaluations

3.2.2.1 Key Secondary Endpoint

- Differences in the number of lesions detected by 68Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. Significant uptake of 68Ga-OPS202 for the evaluation

of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of 68Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.

- The SUV_{mean} and SUV_{max} in the primary lesion between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain); the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.

3.2.2.2 Other Secondary Endpoints

- Differences in relative lesion counts as a ratio of the number of lesions detected by ^{68}Ga-OPS202 at 0.5, 1 and 2 hours post dose respectively, compared to the number of lesions assessed by standard-of-truth (descriptive analyses). The standard-of-truth is the ^{18}F-FDG-PET/CT scan images acquired at any time during the study period (including the Screening period). This will be calculated by (number of lesions detected by ^{68}Ga-OPS202) / (number of lesions detected by ^{18}F-FDG-PET).
- Differences of absolute number of lesions between the three PET acquisition timepoints detected in each of the following anatomic sites:
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
  - Brain

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

The secondary endpoints will be summarised by each of the three PET acquisition timepoints (0.5, 1 and 2 hours).

3.2.3 Exploratory Endpoints

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of breast cancer expressing sstr2 positive by both subject-based and lesion-based analysis compared to standard-of-truth
- SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} at the three PET acquisition timepoints
- Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG-PET
- Estimated correlation between ^{68}Ga-OPS202 PET uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

For further details on efficacy endpoints, refer to Section 7 and the IRC.

3.2.4 Safety Endpoints and Evaluations

The investigator will report the occurrence of any AE throughout the study and vital signs (including blood pressure and heart rate) measurements at each visit: Screening Visit (Visit 1; Day -14 to -1), Visit 2 (Day 1), Visit 2 (Day 2) and End of Study/Early Withdrawal Visit

(Visit 3). Clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis) measurements will be reported at Screening Visit, Visit 2 (Day 2) and End of Study/Early Withdrawal Visit. Physical examination findings and body weight measurements will be reported at Screening Visit, Visit 2 (Day 1) and End of Study/Early Withdrawal Visit. The electrocardiogram (ECG) findings are to be recorded at the Screening Visit and the End of Study/Early Withdrawal Visit. Relevant medical history and concomitant medications/therapies will also be recorded throughout the study.

The following safety endpoints will be evaluated:

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

3.3 Randomisation and Blinding

This is an open-label non-randomised study. However, the independent readers will evaluate ^{68}Ga-OPS202 PET/CT and ^{18}F-FDG-PET/CT images and will be blinded to the acquisition time of the PET scans and CT scans, 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. Two readers will read 100% of all the images and third will adjudicate any differences. See the Imaging Review Charter (IRC).

3.4 Maintenance of Randomisation and Blinding

All blinding is handled by the ICL and described in the IRC.

3.5 Study Imaging Product and Dosage

The IIP is provided in 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 radiolabelling kit must be maintained between + 2 °C and + 8 °C until reconstitution.

Radiolabelling yields the IIP ^{68}Ga-OPS202 as a solution for injection, placed in a shielding secondary container. This shielding container will be labelled according to local requirements and identified with a radiolabelling batch number and the subject number. The volume to be administered to the subject is withdrawn from the IIP vial. This volume is determined to obtain the target radioactivity dose at the time of administration, taking into account the decay of ^{68}Ga. All subjects will receive a single dose of 150-200 MBq ^{68}Ga-OPS202 (IIP), as a slow i.v. bolus injected over 1 minute.

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

The radiolabelling kit will be packaged and delivered in a sufficient quantity to the investigational sites with a delivery note including an acknowledgement of receipt.

The investigator's representative will receive:

- For each batch of radiolabelling kit that will be used during the study, a Certificate of Compliance and Certificate of Analysis, which reflects the product release statement,
- Material Safety Data Sheet,
- Delivery note including an Acknowledgement of Receipt (AoR), Packaging Order.

All the labels identifying the radiolabelling kits will be designed in accordance with all requirements of Good Manufacturing Practice (GMP) and applicable national laws in force in the countries. The label of the radiolabelling kit and the label of lead container will be translated into local languages.

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

3.6 Study Duration

Subject participation in the study will include:

- Visit 1: a screening period up to 14 days prior to IIP administration
- Visit 2: a single i.v. injection of between 150 MBq to 200 MBq of ^{68}Ga OPS202 on Day 1 followed by PET acquisition at 0.5, 1 and 2 hours ±10 minutes post dosing,
- Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety.
  Within the study an ^{18}F-FDG-PET scan and also a ceCT scan must also be acquired.

The subject's participation in the study will be considered to have ended at the time of the last visit (Visit 3, at Day 14 ±3 days).

The overall duration of the study will be approximately 4 weeks for each subject. The study will be considered to have started when the first subject has provided signed informed consent.

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

3.7 Stopping Rules and Discontinuation Criteria

During the conduct of the study, SAEs will be reviewed (see Section 8.1.3) as they are reported from the study centres to identify safety concerns. A specific site or a given cohort can 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.

The study may be terminated by the sponsor at any time.

A subject may discontinue participation in the study at any time for any reason (e.g. withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol deviation as defined in Section 13.1.2, noncompliance with the protocol conditions or AE). All cases of discontinuation will be discussed between the investigator and the sponsor.

Futility Stopping Rule

If less than three sstr2 positive evaluable subject scans out of 30 consecutive subjects screened with ^{68}Ga-OPS202 PET/CT, or less than 8 out of 50, the study will be stopped.

3.8 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 in the eCRF.

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

As required by ICH GCP Section 6.4.9, if some items are recorded directly in 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, competent authorities (CAs). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

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

(1) Women aged 18 years or older

(2) Subjects with newly diagnosed (early or advanced) breast cancer

(3) Eastern Cooperative Oncology Group (ECOG) performance status ≤2

(4) Adequate bone marrow, liver and renal function, with:

- Calculated glomerular filtration rate (GFR): ≥45 mL/min
- Albumin: >30 g/L
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP): ≤5 times upper limit of normal (ULN)
- Bilirubin: ≤3xULN (3×1.1 mg/dL)
- Leukocytes: $\geq 3x10^9$/L, and neutrophils: $\geq 1x10^9$/L
- Erythrocytes: $\geq 3.5x10^{12}$/L
- Platelets: $\geq 90x10^9$/L

(5) Signed written informed consent prior to any study-related procedures.

4.2 Exclusion Criteria

Subjects will be excluded for any of the following reasons:

(1) Subject with resected primary tumour

(2) Subjects with confirmed ductal carcinoma in situ

(3) Men with breast cancer

(4) Presence of an active infection at screening or history of a serious infection within the previous 6 weeks prior to the first ^{68}Ga-OPS202 administration that might interfere with the PET and/or CT analysis

(5) Subjects who have received any therapy for breast cancer

(6) Prior or planned administration of a radiopharmaceutical within 8 half-lives of the radionuclide

(7) Clinically relevant trauma within 2 weeks prior to first ^{68}Ga-OPS202 administration

(8) Any condition that precludes the proper performance of PET and/or CT scan:

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

(9) Known hypersensitivity to radiolabelled NODAGA (1,4,7-triazacyclononane,1-glutaric acid 4,7 acetic acid), to Gallium-68, to somatostatin analogue peptide JR11 or to any of the excipients of ^{68}Ga-OPS202

(10) History of, or current active allergic or autoimmune disease, including asthma or any condition requiring long-term use of systemic corticosteroids

(11) Known human immunodeficiency virus (HIV) or positive serology for HIV, hepatitis B or C

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

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

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

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

4.3 Rationale for Inclusion/Exclusion Criteria

Eligibility criteria include those that define subjects with breast cancer eligible for imaging with ^{68}Ga-OPS202 PET/CT scan. There is no upper limit for age since eligibility criteria exclude conditions that could affect elderly participation in the study.

4.4 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (and 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, pregnancy (see Section 8.1.4) 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 3.7, 5.2.5, 6.2 and 8.1.6.

If a subject decides to withdraw from the study after the administration of IIP, or 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 5.2.5) 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 in 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, the subject is referred to the care of a local health care professional, or a determination of a cause unrelated to the IIP or study procedure is made. The specific AE or test result(s) must be recorded in the eCRF. All evaluations should be performed, according to the protocol, on the day the subject receives IIP, or as soon as possible thereafter.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 3.

Table 3 Study Procedures and Assessments

Study Visits [a]	Screening Visit 1 Day -14 to -1	Visit 2[a] Day 1	Visit 2[a] Day 2	End of Study/Early Withdrawal Visit 3 Day 14 (±3)
Informed consent [b]	X			
Eligibility criteria	X	X		
Demographics [c]	X			
Medical history [d]	X			
Prior therapies [d]	X			
Concomitant therapies [e]	X	X	X	X
Physical examination [f]	X	X		X
Vital signs [g]	X	X	X	X
ECG [h]	X			X
Haematology [i]	X		X	X
Blood chemistry [j]	X		X	X
Urinalysis [k]	X		X	X
Pregnancy test [l]	ßHCG (blood test)	Urinary HCG		ßHCG (blood test)
^{68}Ga-OPS202 PET/CT imaging [m]		X		
^{18}F-FDG-PET scan [n]	Any time during the study period			
Contrast enhanced CT [m]	With ^{68}Ga-OPS202 PET or ^{18}F-FDG-PET			
Adverse events [o]	X	X	X	X
Compliance [p]		X		
Biopsy [q]	X			

AE=adverse event, CT=computed tomography, ECG=electrocardiogram, ^{18}F-FDG=^{18}F-fluorodeoxyglucose, HCG=human chorionic gonadotropin, HER2= human epidermal growth factor receptor 2, ICL=imaging core laboratory, IIP=investigational imaging product, PET=positron emission tomography.

(a) **Study visits**: Screening Visit up to 14 days before IIP administration; Subjects may be hospitalised overnight at the discretion of the investigator at Visit 2. All subjects (either hospitalised or not) will attend consultation on Day 2, which is part of Visit 2, for: review of AEs, new or changed concomitant medications, vital signs, haematology, biochemistry, urinalysis.

(b) **Informed consent**: Must be obtained prior to undergoing any study specific procedures and will occur prior to the 2-week screening period.

(c) **Demographics**: Age, sex and self-reported race/ethnicity if authorised to be collected in the country.

(d) **Medical history and prior therapies**: To include clinically significant diseases, surgeries, cancer history and all relevant medications.

(e) **Concomitant medications**: Dose and indication will be recorded from 3 months prior to the IIP administration, at study entry and at each visit. Once the subject has withdrawn from/completed the study, concomitant medications and treatments should be recorded until all study treatment-related toxicities have resolved.

(f) **Physical examination**: Major body systems, body weight, height (screening visit only).

(g) **Vital signs**: pre-dose and at 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure and heart rate, body temperature, respiratory rate).

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

(i) **Haematology**: Red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

(j) **Blood chemistry**: urea, creatinine, creatinine clearance, chloride, bicarbonate, sodium, potassium, calcium, phosphate, total bilirubin, conjugated bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose.

(k) **Urinalysis**: Dipstick for pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocyte esterase, glucose and specific gravity.
(l) **Pregnancy test:** A pregnancy test will be performed at each visit particularly before ^{68}Ga-OPS202 administration.
(m) **^{68}Ga-OPS202 PET/CT imaging**: PET acquisition at 0.5, 1 and 2 hours after ^{68}Ga-OPS202 administration. Iodinated i.v. CT contrast imaging (chest, abdomen, pelvis and brain). A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained (see the Imaging Review Charter (IRC)). Anonymised and blinded to acquisition time images will be sent to the ICL.
(n) **^{18}F-FDG-PET scan**: ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be performed during the study period and images sent to ICL. A ceCT or a low dose CT may be performed with the ^{18}F-FDG-PET (see the IRC)
(o) **Adverse events**: Subjects must be followed for AEs, regardless of relationship to IIP, from the time they signed the informed consent until 14±3 days after the dose of IIP. Clinically significant changes in physical examination, vital signs, electrocardiogram and laboratory findings will be recorded as an AE. The investigator will follow-up AEs until resolution or stabilisation.
(p) **Compliance**: The peptide mass dose and the radioactivity dose injected will be recorded at Visit 2.
(q) **Biopsy:** To be performed if not already done. Tumour biopsy, which is not a prerequisite for inclusion, is routinely performed for confirmation and staging of the disease, as well as classification according to hormone receptor status and HER2 status. For the study, an archived tumour sample (block is preferred over paraffin embedded slides) is required for the evaluation of sstr2 expression by immunohistochemistry staining.

5.2 Study Visits

5.2.1 Procedures for Screening and Enrolment (Visit 1)

A signed and dated informed consent form will be obtained before screening procedures begin.

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

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

The screening visit (Visit 1) will be performed within 14 days prior to the first ^{68}Ga-OPS202 administration. The following assessments will be performed:

- Eligibility check (inclusion/exclusion criteria)
- Demographic data (age, sex and self-reported race/ethnicity according to individual country regulations/requirements and if authorised in the country). The collection of these data is needed to establish whether or not there are potentially clinically important sex- and racial/ethnic-based differences in the anticipated effects of the studied product
- Medical history (including clinically significant diseases, surgeries, cancer history)
- Physical examination
- Vital signs (body temperature, supine and standing systolic and diastolic blood pressure, heart rate, respiratory rate)
- Body weight and height
- ECG (recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available)
- Laboratory safety tests (blood sampling for haematology, biochemistry, and urinalysis)

- Beta human chorionic gonadotropin (ß-HCG) pregnancy test for women of childbearing potential
- Prior and concomitant medications/therapies
- Collection of AEs after signed informed consent has been obtained
- Collection of historical paraffin embedded breast tumour blocks or slides with anatomical location of the lesion indicated
- ^{18}F-FDG-PET scan (which can also be performed at any time during the study period, including the Screening period).

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

5.2.2 Procedures Before Study IIP Administration (Day 1, Visit 2 Pre-dose)

The following procedures will be performed on Day 1, prior to the IIP administration:

- Eligibility check (inclusion/exclusion criteria)
- Vital signs (body temperature, supine and standing blood pressure, heart rate and respiratory rate)
- Physical examination (including body weight)
- Pregnancy test (urine)
- Concomitant therapies
- Review of AEs.

5.2.3 Dosing (Day 1, Visit 2)

The following procedures will be performed at Visit 2 Day 1:

- One injection of ^{68}Ga-OPS202 (Dosing)

5.2.4 Procedures after IIP Administration (Day 1 and Day 2, Visit 2 Post-dose)

The following procedures will be performed at Visit 2 Day 1 post-dose:

- Whole body PET imaging at 0.5, 1 and 2 hours after the injection of the IIP
- A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired with PET scans when necessary for attenuation correction. See IRC for further details.
- Review of AEs
- New or changed concomitant medications
- Vital signs at 0.5, 1, 2 and 4 hours post-injection (body temperature, supine and standing blood pressure, heart rate and respiratory rate).

Subjects may be hospitalised overnight at the discretion of the investigator. All subjects (either hospitalised or not) will attend consultation on Day 2, which is part of Visit 2.

On Day 2, the investigator will evaluate if the subject is fit to be discharged home. Subjects who are not hospitalised will return to the investigator site on Day 2.

The following procedures will be performed at Visit 2 Day 2:

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

Upon discharge from the hospital on Visit 2 (Day 2), the subject will be asked to return to the study site on Day 14 (±3 days) for safety follow-up (Visit 3).

5.2.5 End of Study Visit or Early Withdrawal Visit (Day 14±3, Visit 3)

The subject's participation in the study will be considered to have ended at the time of the last visit (Visit 3, at Day 14±3 days).

For subjects who complete the study, final evaluations will be performed on Day 14 (±3 days) after the subject receives the IIP. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2, respectively.

The following procedures will be performed at the End of Study (Visit 3, Day 14±3 days) or Early Withdrawal visit:

- Review of AEs
- New or changed concomitant therapies
- Physical examination including body weight
- Vital signs (body temperature, supine and standing blood pressure, heart rate and respiratory rate)
- ECG (recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available)
- Clinical laboratory tests (blood sampling for haematology and biochemistry, and urinalysis)
- Pregnancy test (ßHCG blood test).

6 INVESTIGATIONAL IMAGING PRODUCT AND DOSING OF SUBJECTS

6.1 Investigational Imaging Product Preparation and Radiolabelling Kit, Storage and Accountability

6.1.1 Investigational Imaging Product and Radiolabelling Kit Storage and Security

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

6.1.1.1 Spillage

All due precautions and site procedures should be implemented to prevent spillage or leakage of radiodiagnostics. Syringes, intravenous lines, venous access should all be secured and the

connections thoroughly checked. The injection/infusion line should be taped in a loop and taped to the subject to prevent direct tension between the line and the venous access.

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

6.1.2 Investigational Imaging Product Preparation

The investigator, or an approved representative (e.g. pharmacist), will ensure that all IIP are reconstituted, radiolabelled and dispensed by qualified staff members.

6.1.3 Investigational Imaging Product and Radiolabelling Kit Accountability

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

The destruction of used and unused radiolabelling kit and IIP should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. The study radiolabelling kits, IIP and any other study related material will be destroyed on site.

6.1.4 Investigational Imaging Product (^{68}Ga-OPS202)

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

- JR11, an antagonist somatostatin analogue that binds to sstr2 receptors
- NODAGA, a chemical chelator moiety and
- ^{68}Ga, a positron-emitting radionuclide with a half-life of 68 minutes.

The IIP is a solution for injection prepared prior to administration from a radiolabelling "cold" kit and a ^{68}Ge/^{68}Ga-generator. The OPS202 peptide is provided in a sterile two-vial radiolabelling kit constituted of:

- freeze-dried lyophilised 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) (one kit per subject dose) 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 prior to radiolabelling of Vial A and Vial B,
- Radiolabelling of the precursor OPS202 achieved by the addition of a 6-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 dose at the time of administration, taking into account the decay of ^{68}Ga. All subjects will receive a single dose of 150-200 MBq ^{68}Ga-OPS202 (IIP), as a slow i.v. bolus injected over 1 minute.

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 dose injected to subject. In addition, any extravasation during infusion should be measured and this radioactivity deducted from the calculated amount injected into the subject.

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

6.2 Study Drugs Administered

^{68}Ga-OPS202 is prepared, up to 3 hours prior to administration, by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit containing 50 µg of peptide.

6.3 Concomitant Medication/Therapy

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

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

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

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

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

6.4 Procedures for Monitoring Subject Compliance

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

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

7 ASSESSMENT OF EFFICACY

For the primary, secondary and exploratory endpoints all the sets of images obtained at Visit 2 and one ^{18}F-FDG-PET and one ceCT scan will be sent to an ICL for quality control and management of the reads. The centralised reads will be undertaken by two independent experienced radiologists and/or nuclear medicine physicians, and a third for adjudication of discordances for most of the reads. The readers will be specifically trained for this protocol. Full details of the read design and conduct will be provided in the IRC.

For the primary endpoint analysis, the number of lesions and quality of the images will be taken into consideration by the readers. Scans will be blinded to subject identification, site and timing post injection. No adjudication will be conducted as inter-reader differences will be part of the evaluation.

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

(1) Review of the three image sets of ^{68}Ga-OPS202 scans in randomised fashion, with CT image fusion. The ceCT images acquired will be used for co-registration. Two readers will read and a third will adjudicate any differences.

(2) ^{18}F-FDG-PET images for standard-of-truth assessments will be reviewed by two radiologists not involved in ^{68}Ga-OPS202 PET/CT images read, and the lesions mapped to the ^{68}Ga-OPS202 read. Two readers will read and a third will adjudicate any differences.

(3) SUV_{max} and SUV_{mean} calculations of the five most avid lesions per organ on ^{68}Ga-OPS202 PET scans (primary breast lesion, liver, lymph nodes, bone, lungs and brain) will be conducted by the ICL after identification of the lesions by one of the primary readers.

(4) Review of the lesion-to-background ratios in each major anatomical site (primary breast lesion, liver, lymph nodes, bone, lungs and brain) based on the evaluation of up to five most avid lesions per organ will be managed by the ICL after the lesions have been identified by one of the primary readers.

(5) For image quality, direct comparison of the three ^{68}Ga-OPS202 scans acquired at different times, will be conducted for the primary breast cancer and then for all other lesions as the final step of the blinded read. The readers will be allowed to select whether one, two or all three acquisitions are optimal. The readers will be blinded to time point sequence. No adjudication will be required.

(6) The ^{68}Ga-OPS202 PET scans will be compared with the ^{18}F-FDG-PET scan (with ceCT).

(a) Primary Efficacy Endpoint and Evaluation

The co-primary endpoint is therefore calculated in the following way:

(1) The number of subjects with newly diagnosed breast cancer with primary sstr2 positive lesions identified by ^{68}Ga-OPS202 at any timepoint, divided by the total number of subjects imaged to obtain the prevalence in this study population.

(2) The identification of the optimum acquisition time(s) based on differences in the number of lesions identified at each scan, and the reader interpretation of the optimum image in the primary breast lesions. The optimum image acquisition time could be one, two or all three acquisitions timepoints i.e. no noticeable difference between 0.5, 1 and 2 hours post infusion.

(b) Secondary Efficacy Endpoints and Evaluations

Key Secondary Endpoint:

- Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.
- The SUV_{mean} and SUV_{max} in the primary lesion between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain); the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.

Other Secondary Endpoints:

- Comparison to standard-of-truth for the primary breast tumour:
  - (^{68}Ga-OPS202 PET/CT) / (^{18}F-FDG-PET/CT)
  - For each acquisition time of ^{68}Ga-OPS202 PET.

  This will be repeated for each of the other anatomical locations:
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
  - Brain

The second component of the co-primary and appropriate secondary endpoints will also be evaluated on a radioactivity dose MBq/kg of body weight to evaluate if the subject mass has an effect on the diagnostic accuracy.

Exploratory Endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging sstr2 positive breast cancer tumours by both subject-based and lesion-based analysis compared to standard-of-truth
- SNR calculated from: SUV_{mean}/SUV_{SD} at the three PET acquisition timepoints using the same lesions as for SUV_{max}. The background will be the same background as for SUV_{max}, of either lesion-free volume of interest (VOI) in the liver or aorta, if insufficient lesion free liver is available
- Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG PET scan. This will be based on lesion counts off the identified optimal timepoint or from the 1-hour timepoint if no optimum is identified
- Estimated correlation between tumour uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

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

(c) Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

Methods for assessing efficacy data are listed below and are described in further detail in the IRC. Timing of efficacy acquisitions are discussed in Section 5. The efficacy data are obtained from the ICL and will be obtained using electronic means. The methods of analyses are discussed in Section 11.4.4.

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

- All ^{68}Ga-OPS202 PET/CT scans
- One ^{18}F-FDG-PET/CT scan.
- One ceCT scan.

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

- Full acquisition guidelines for the site, for IIP and ceCT scan
- Process for PET scanner quality control (phantom assessments and reporting)
- Image transmission methodology
- Core lab QC methodology and management of the images
- Read design for primary endpoint
- Read design for secondary endpoint and process for calculating tumour-to-background ratio and SUV_{mean} and SUV_{max}
- Design of exploratory endpoints
- Conduct of the read
- Management, training and inter-reader evaluation
- Data management
- Data export overview
- Archiving of images.

7.1 Eligible and Evaluable Subjects

- All subjects who receive ^{68}Ga-OPS202 are “eligible” subjects and will be included in the safety analysis.
- All eligible subjects with one or more readable ^{68}Ga-OPS202 PET and a readable ceCT scan will be included in the first component of the co-primary endpoint analysis to determine sstr2 positive prevalence.
- The following describes those subjects that are eligible and “evaluable” for the second component of the co-primary endpoint to assess the optimum timing of the PET scan following infusion of ^{68}GaOPS202:
  - A readable ceCT scan
  - At least two ^{68}Ga-OPS202 PET scans that are readable (three images are to be acquired but 2 of these, MUST be readable by the central readers; if only two PET scans are acquired BOTH must be readable) with at least one avid lesion identified by central readers.

8 ASSESSMENT OF SAFETY

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

- AEs throughout the study
- Clinical laboratory test results (serum chemistry, haematology, urinalysis) throughout the study
- Vital signs measurements (blood pressure and heart rate) throughout the study
- ECG at Visit 1 (Screening) and Visit 3 (End of treatment/Early Withdrawal)
- Physical examination results throughout the study
- Concomitant medication usage throughout the study.

8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study (see Section 3.6 for a definition of the study duration) and will be elicited by direct, nonleading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.1.

Definition of an Adverse Event

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

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.6).

8.1.1 Categorisation of Adverse Events

8.1.1.1 Intensity Classification

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

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

Where:

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

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

8.1.1.2 Causality Classification

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

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

8.1.1.3 Assessment of Expectedness

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

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

8.1.1.4 Laboratory Test Abnormalities

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

- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the investigator, or the laboratory test abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline based on sponsor review.

8.1.1.5 Abnormal Physical Examination Findings

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

8.1.1.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g. electrocardiogram changes) or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.2 Recording and Follow up of Adverse Events

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

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

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs,

sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IIP or other illness). The investigator is required to assess causality and record that assessment in the eCRF. Follow-up of the AE, after the date of IIP discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.

8.1.3 Reporting of Serious Adverse Events

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

An SAE is any AE that:

(1) Results in death,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.1.4 Pregnancy

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

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

The investigator must instruct all subjects to inform them immediately should they become pregnant during the study. In case the investigator becomes aware of pregnancy occurring in a subject (pregnancy test before exposure to the IIP), the IIP should not be administered and the subject followed up until Visit 3 (End of the study). The investigator should counsel the subject, discuss the risks, if any, and the possible effects on the foetus. Monitoring of the subject who becomes pregnant during the study after the administration of the single IIP injection should continue until conclusion of the pregnancy, which may involve follow up after the subject's involvement in the study has ended (as per Ipsen's standard pharmacovigilance).

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

8.1.5 Deaths

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

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

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

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

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

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

Reporting to Competent Authorities/IECs/IRBs/Other Investigators

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

8.2 Clinical Laboratory Tests

Blood samples will be collected at all study visits (Screening Visit [Visit 1], Day 2 [Visit 2], and End of Study/Early Withdrawal [Visit 3]) (see schedule of assessment in Table 3) for the evaluation of haematology and serum chemistry.

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

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

8.2.1 Haematology

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

8.2.2 Blood Biochemistry

Blood samples will be collected at all visits to assess the following parameters:

- urea, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin
- chloride, bicarbonate, sodium, potassium, calcium, phosphate
- AP, AST, ALT, GGT
- albumin, total protein, total cholesterol, triglycerides, fasting glucose.

8.2.3 Urinalysis

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

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

8.2.4 Pregnancy Test

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

8.2.5 Putative Antibody Testing

No putative antibody testing is planned.

8.2.6 Other Clinical Laboratory Tests

No other clinical laboratory tests are planned.

8.3 Physical Examination

Physical examinations, including body weight, will be conducted at Screening (Visit 1), IIP administration visit (Visit 2 only on Day 1) and End of Study (Visit 3)/Early Withdrawal (see Table 3), and height will be measured at Screening.

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

8.4 Vital Signs

Blood pressure and heart rate will be assessed at Screening (Visit 1), IIP administration visit (Visit 2: Day 1 pre-dose and at 0.5, 1, 2, 4 hours post-injection and on Day 2), and End of Study (Visit 3)/Early Withdrawal (see Table 3), with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes rest in sitting position and after one minute standing. Absolute values and change from Baseline will be analysed.

Respiratory rate and temperature (tympanic/oral) will be recorded at the same timepoints.

8.5 Electrocardiography

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

The ECGs will be recorded at Screening Visit (Visit 1), and End of Study/Early Withdrawal (Visit 3).

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

Any clinically significant abnormalities will be recorded as AEs.

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

10 EXPLORATORY BIOMARKERS AND BIOBANKING

No exploratory biomarker collection or biobanking are included in this protocol.

11 STATISTICS

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 the dose of study IIP.
- **^{68}Ga-OPS202 screened population**: All subjects who received the dose of study IIP and for whom PET/CT scan images are readable for at least one timepoint. This population encompasses both subjects with sstr2 positive lesion(s) and those with sstr2 negative lesions (no avid lesion with ^{68}Ga-OPS202).
- **Sstr2 positive population:** All subjects who received the dose of study IIP and for whom ^{68}Ga-OPS202 PET/CT scan images are readable for at least one timepoint and have one avid lesion identified by central readers, ^{18}F-FDG-PET/CT scan and a ceCT scan confirmed by the central readers.
- **Sstr2 positive evaluable population:** ^{68}Ga-OPS202 sstr2 positive population with at least two evaluable ^{68}Ga-OPS202 timepoints, ^{18}F-FDG-PET/CT scan and a ceCT scan confirmed by the central readers.

11.1.1 Populations Analysed

The co-primary analysis based on the primary efficacy endpoint to determine sstr2 positive percentage will use the ^{68}Ga-OPS202 screened population as the denominator. The co-primary analysis based on the primary efficacy endpoint to assess optimum imaging timing of the PET scan following ^{68}Ga-OPS202 injection will be performed on the sstr2 positive evaluable population. In addition, secondary/confirmatory analysis may be performed on the sstr2 positive population.

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

11.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

The reasons for subject exclusions from each of the populations will be listed and tabulated.

11.2 Sample Size Determination

It is anticipated that a total of approximately 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 PET/CT imaging, to obtain around 16 sstr2 positive BC evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be administered ^{68}Ga-OPS202 in the study will be over 50. However, when the ICL identifies 16 sstr2 positive evaluable subjects, with a minimum of two subjects with advanced disease, the study will be complete.

This estimation of 16 sstr2 positive BC evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited as a replacement to ensure an adequate sample size in the sstr2 positive BC evaluable set.

11.3 Significance Testing and Estimations

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

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the sponsor's Biometry Department.

A Statistical Analysis Plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings 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 Statistical Analysis System (SAS)® (version 9.2 or higher).

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (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 safety, sstr2 positive evaluable and sstr2 positive populations.

11.4.2 Homogeneity of Treatment Groups

Not applicable.

11.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects screened, enrolled and included in each of the sstr2 positive evaluable, sstr2 positive 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 IIP at Visit 2, discontinued and completed the study will be tabulated. Primary reasons for discontinuation of study IIP will be listed and tabulated.

11.4.4 Efficacy Evaluation

As indicated in Section 7, the first component of the co-primary endpoint is the percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. This will be a simple percentage calculation (number of subjects in sstr2 positive population / number of subjects in ^{68}Ga-OPS202 screened population). The second component of the co-primary efficacy variable is the differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours) in the primary breast lesions. The second component of the co-primary efficacy variable will be summarised by each of the three PET acquisition timepoints (0.5, 1 and 2 hours). The results could identify that one, two or all three timepoints have equal validity for future studies in this population.

As indicated in Section 7, the secondary efficacy variables are the variables measured at Visit 2 after the i.v. administration of the IIP, listed below:

Key Secondary Endpoint:

- Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours) and reader interpretation of optimal image(s) in nodular and metastatic lesions. Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.
- The SUV_{mean} and SUV_{max} in the primary lesion between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed by

the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain); the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.

Other Secondary Endpoints:

- Differences in relative lesion counts as a ratio of the number of lesions detected by ^{68}Ga-OPS202/ceCT at 0.5, 1 and 2 hours post dose respectively, compared to the number of lesions assessed by standard-of-truth (descriptive analyses). The standard-of-truth is the ^{18}F-FDG-PET/CT scan images acquired at any time during the study period (including the Screening period). This will be calculated by (number of lesions detected by ^{68}Ga-OPS202) / (number of lesions detected by ^{18}F-FDG-PET).
- Differences of absolute number of lesions between the three PET acquisition timepoints detected in each of the following anatomic sites:
  - Lymph nodes
  - Liver
  - Axial/appendicular skeleton
  - Lungs
  - Brain

The second component of the co-primary and appropriate secondary endpoints will also be evaluated on a radioactivity dose MBq/kg of body weight.

The secondary endpoints will be summarised by each of the three PET acquisition timepoints (0.5, 1 and 2 hours).

Exploratory Endpoints:

- Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging of breast cancer expressing sstr2 positive by both subject-based and lesion-based analysis compared to standard-of-truth
- SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} at the three PET acquisition timepoints
- Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG-PET
- Estimated correlation between ^{68}Ga-OPS202 PET uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

For further details on efficacy endpoints, refer to Section 7 and the Imaging Review Charter (IRC).

11.4.5 Adjustment for Country/Centre Effect

Not applicable.

11.4.6 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 Drug Dictionary (WHO-DD) (latest available version) and will be summarised.

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs (including blood pressure and 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.

11.5 Subgroup Analyses

Not applicable.

11.6 Interim Analyses

No interim analysis will be performed.

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

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

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Protocol Amendments and Protocol Deviations and Violations

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, 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

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

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

Generally, a protocol deviation qualifies as major if:

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

See Section 11.1.2 for details on the impact of major protocol deviations on the inclusion of subjects in each analysis population.

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

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

13.2 Information to Study Personnel

To ensure accurate, complete and reliable data, the sponsor or its representatives will provide instructional material to the study sites, as appropriate. A study initiation visit will be conducted prior to screening start to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the 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, or new information becomes available). The investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

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

13.3 Study Monitoring

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

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

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

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

13.4 Audit and Inspection

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

13.5 Data Quality Assurance

Monitored eCRFs will be reviewed (secondary monitoring) by the assigned Data Management group for completeness, consistency, legibility and protocol compliance.

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

14 ETHICS

14.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines.

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 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 that they comply with GCP requirements. The IEC approval must identify the protocol version as well as the documents reviewed.

After IEC 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 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.

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). Sufficient time will be allowed to discuss any questions raised by the subject.

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

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

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

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) (EC) 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 eCRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

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

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 administration, laboratory data, safety data in the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF.

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

All corrections in 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

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

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the contracted CRO standard operating procedures (SOPs), unless otherwise specified. Prior to data being received in-house at the assigned CRO, they will be monitored at the investigator site; for further details please see Section 13.3 Monitoring Procedures. The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

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

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

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

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

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

Only data from enrolled subjects will be reported in the eCRFs and collected in the sponsor's database.

For screen failure subjects, only the Unique Subject Identifier, the date of informed consent signature, the reason why 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 pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

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

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

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

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

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

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.

18 REFERENCES

1. Octreoscan™ Prescribing Information. [available at: https://www.drugs.com/pro/octreoscan.html, accessed 01 November 2017].
2. NETSPOT® Prescribing Information. [available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208547s000lbl.pdf, accessed 01November 2017].
3. Summary of Product Characteristics SomaKit TOC 40 micrograms kit for radiopharmaceutical preparation. [available at: http://www.adacap.com/wp-content/uploads/2017/05/emea-combined-h-4140-en.pdf, accessed 01 December 2017].

19 LIST OF APPENDICES

Appendix 1 Protocol Summary of Changes - Amendment 1.0

STUDY NUMBER	D-FR-01070-003
PROTOCOL TITLE:	A non-randomised phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 2.0, Amendment 1.0; 27 June 2018

THE FOLLOWING AMENDMENTS ARE PROPOSED:

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1	Title page	Version 1.0; 02 February 2018	Version 2.0, Amendment 1.0; 27 June 2018
		Sponsor Signatory: PPD	**Sponsor Signatory:** PPD
1	Title page	**Emergency Contact:** PPD Ipsen Biopharm Ltd, 102 Park Drive, Milton Park, Abingdon, OX14 4RY, UK. Tel: PPD Mobile: PPD The person listed above is ~~designated~~ by the sponsor as the first point of contact for emergency situations. For serious adverse events (SAEs) reporting: Email: PPD	**Pharmacovigilance/Emergency Contact:** PPD , Ipsen Innovation ZI de Courtaboeuf - 5 avenue du Canada - 91940 Les Ulis - France Phone: PPD Mobile: PPD The person listed above is **medically qualified and designated** by the sponsor as the first point of contact for emergency situations. For serious adverse events (SAEs) reporting: Email address **(preferably)**: PPD Fax: PPD
4	Synopsis	**Planned study period**: FPI: ~~April~~ 2018 - LPO: December 2018	**Planned study period**: FPI: **July** 2018 - LPO: December 2018
4	Synopsis	**Study hypothesis:** The ~~update~~ of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.	**Study hypothesis:** The **uptake** of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.

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5	Synopsis	**Methodology**: *Study design:* ... Three PET ~~images~~ will be ~~acquired~~ at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection ~~and one contrast enhanced (ce) CT scan will also be acquired at 2 hours post PET timepoint.~~ All images will be sent to an imaging core laboratory (ICL) for central blinded reading ~~by two independent experienced radiologists/nuclear medicine physicians and a third for adjudication of discordances. The readers will be specifically trained for this protocol~~. ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards.~~ ^{18}F-FDG-PET scan images will also be sent to the ICL.~~	**Methodology:** *Study design:* ... Three PET **acquisitions** will be **performed** at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection. ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards. **A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Thus, only one ceCT scan is required to minimise radiation dose. Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained.** All images **(^{68}Ga-OPS202 PET/CT scans, ^{18}F-FDG-PET scan, and ceCT scan)** will be sent to an imaging core laboratory (ICL) for central blinded reading.
5	Synopsis	*Duration of participation for a subject:* ... • Visit 2: a single intravenous (i.v.) injection of a fixed activity range of ^{68}Ga-OPS202 ~~on Day 1~~ followed by PET ~~imaging~~ at 0.5, 1 and 2 hours ±~~5~~ minutes post dosing~~, and a ceCT scan immediately after the 2-hour PET timepoint~~ • Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety.	*Duration of participation for a subject:* ... • Visit 2 **(Day 1)**: a single intravenous (i.v.) injection of a fixed activity range of ^{68}Ga-OPS202 followed by PET **acquisitions** at 0.5, 1 and 2 hours ±**10** minutes post dosing **(see Methodology Section above)** • Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety. **Within the study an ^{18}F-FDG-PET scan and also**

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			a ceCT scan must also be acquired.
5-6	Figure S1	Figure contains strata per invasive stage. Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 evaluable subject scans~~: eight subjects with early disease and eight subjects with advanced disease~~.	Strata removed from figure and footnotes updated. Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 **positive** evaluable subject scans.
6	Synopsis	*Assessments:* The Screening Visit (Visit 1) will be performed within 14 days prior to the first ^{68}Ga OPS202 administration. At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination, laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available. Tumour biopsy~~, which is not a prerequisite for inclusion, is routinely performed for confirmation and staging of the disease, as well as classification according to hormone receptor status and human epidermal growth factor receptor 2 (HER2) status. For the study, paraffin embedded slides are~~ required for the evaluation of sstr2 expression by immunohistochemistry staining. Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET imaging at 0.5, 1 and 2 hours after the injection of the IIP. ~~A single ceCT scan will be performed after the 2 hour PET scan, according to the site standard procedure for chest, abdomen, pelvis and brain.~~	*Assessments:* The Screening Visit (Visit 1) will be performed within 14 days prior to the first ^{68}Ga-OPS202 administration. At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination **and vital signs**, laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available. Tumour biopsy **blocks or slides are** required for the evaluation of sstr2 expression by immunohistochemistry staining **with the anatomical location of the lesion(s) indicated to be matched with the ^{68}Ga-OPS202 PET/CT images**. Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET imaging at 0.5, 1 and 2 hours after the injection of the IIP. **An ^{18}F-FDG-PET scan will be acquired at any time during the study period (including the Screening period), according to the investigator**

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		Subjects may be hospitalised overnight upon completion of ^{68}Ga-OPS202 PET/CT scan at the discretion of the investigator.	**site's standards. If the ^{18}F-FDG-PET scan is performed before the informed consent signature, subject approval is required for using this image set.** **A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired with PET scans when necessary for attenuation correction.** Subjects may be hospitalised overnight upon completion of ^{68}Ga-OPS202 PET/CT scan**s** at the discretion of the investigator.
7	Synopsis	**Independent read of PET/CT images:** This is ~~an~~ open-label study. Independent readers will evaluate ^{68}Ga-OPS202 PET/CT and ^{18}F-FDG-PET images and will be blinded to the acquisition time of the PET scan, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical exam findings. ~~I~~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.	**Independent read of PET/CT images:** This is a **non-randomised** 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 acquisition time of the PET scan**s and CT scans**, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical exam findings. **The i**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. **Two readers will read 100% of all the images and third will adjudicate any differences.**
7	Synopsis	**Number of subjects planned**:	**Number of subjects planned**:

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		~~It is anticipated that a total of 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 screening, to obtain around 16 sstr2 evaluable subjects.~~ Considering the estimated prevalence of sstr2 overexpression in breast cancer, ~~the overall number of subjects to be screened with ^{68}Ga-OPS202 in the study will be~~ approximately 54. However, when the ICL identifies 16 sstr2 evaluable subject scans, with ~~eight subjects having early disease and eight~~ subjects advanced disease, the study will be complete. ~~This estimation of 16 sstr2 evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited as a replacement to ensure an adequate sample size in the sstr2 evaluable set.~~	Considering the estimated prevalence of sstr2 overexpression in breast cancer, **it is anticipated that a total of** approximately 54 **subjects will be enrolled in the study for ^{68}Ga-OPS202 PET/CT imaging, to obtain 16 sstr2 positive breast cancer (BC) evaluable subjects.** However, when the ICL identifies 16 sstr2 **positive** evaluable subject scans, with **a minimum of two** subjects **with** advanced disease, the study will be complete. **Futility Stopping Rules** **If less than three sstr2 positive evaluable subject scans out of 30 consecutive subjects screened with ^{68}Ga-OPS202 PET/CT, or less than 8 out of 50, the study will be stopped.** **The Sponsor may consider stopping subject recruitment and revisit the study design with possible termination of the study when justified.**
8-9	Synopsis	**Test product, dose, mode of administration:** ... 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.	**Test product, dose, mode of administration:** ... 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 **50 µg** lyophilised OPS202 and excipients and a second containing a solution for reconstitution.
9	Synopsis	**Reference therapy, dose and mode of administration**: **Comparator compound/placebo**: In this study, there is no comparison with a reference-imaging product. The primary statistical analyses will evaluate the differences (if any) between the three different timepoints	**Reference therapy, dose and mode of administration**: **Comparator compound/placebo**: In this study, there is no comparison with a reference-imaging product. The primary statistical analyses will evaluate the differences (if any) between the three different **scan acquisition**

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		of the ^{68}Ga-OPS202 PET ~~and the PET/CT imaging acquisition~~.	timepoints of the ^{68}Ga-OPS202 PET.
9	Synopsis	**Criteria for evaluation (endpoints)**: Efficacy: The primary and secondary imaging endpoints will be read by third-party independent readers. ~~Most of the reading will be conducted in a blinded manner by two primary readers and a third to adjudicate any differences.~~ Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain. *Co-primary efficacy endpoints and evaluation* • Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202~~)~~	**Criteria for evaluation (endpoints)**: Efficacy: The primary and secondary imaging endpoints will be read by third-party independent readers. Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain. *Co-primary efficacy endpoints and evaluation* • Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the **acquisition** timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 **and 1.5-fold or greater uptake than the non-tumoural liver and lung parenchyma).**
10	Synopsis	*Key secondary endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. • ~~Differences at each of the three timepoints in SUV_{mean} and SUV_{max}, as measured~~ by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain).	*Key secondary endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. **Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.**

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			• **The SUV_{mean} and SUV_{max} in the primary lesions between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed** by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain)**; the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.**
11	Synopsis	*Sample size and power considerations:* It is anticipated that a total of 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 ~~screening~~, to obtain around 16 sstr2 evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be screened with ^{68}Ga-OPS202 in the study will be ~~approximately 54~~. However, when the ICL identifies 16 sstr2 evaluable subjects, with ~~eight subjects having early disease and eight~~ subjects advanced disease, the study will be complete. This estimation of 16 sstr2 evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited ~~as a replacement~~ to ensure an adequate sample size in the sstr2 evaluable set.	*Sample size and power considerations:* It is anticipated that a total of **approximately** 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 **PET/CT imaging**, to obtain around 16 sstr2 **positive BC** evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be screened with ^{68}Ga-OPS202 in the study will be **over 50**. However, when the ICL identifies 16 sstr2 **positive** evaluable subjects, with **a minimum of two** subjects **with** advanced disease, the study will be complete. This estimation of 16 sstr2 **positive BC** evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited to ensure an adequate sample size in the sstr2 **positive BC** evaluable set.

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18		**LIST OF ABBREVIATIONS**	**LIST OF ABBREVIATIONS** Added: **BC Breast cancer** **IRC Imaging review charter** **PT Preferred term**
23	2.3	**Study Hypothesis** The ~~update~~ of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.	**Study Hypothesis** The **uptake** of ^{68}Ga-OPS202 does not vary according to PET acquisition time within a range of 1.5 hours in subjects with sstr2 positive newly diagnosed breast cancer, taking into account the ^{68}Ga decay.
24	3.1	**General Design and Study Schema** ... Three PET images will be acquired at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection ~~and one contrast-enhanced (ce) CT scan will also be acquired at 2 hours post PET timepoint.~~ All images will be sent to an imaging core laboratory (ICL) for central blinded reading ~~by two independent experienced radiologists and/or nuclear medicine physicians and a third for adjudication of discordances. The readers will be specifically trained for this protocol.~~ ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards. ~~^{18}F-FDG-PET scan images will also be sent to the ICL.~~ ...At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination, laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available.	**General Design and Study Schema** ... Three PET images will be acquired at 0.5, 1.0 and 2.0 hours post ^{68}Ga-OPS202 injection. ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be acquired at any time during the study period (including the Screening period), according to the investigator site's standards. **A single ceCT scan is required for the study. This can be acquired following either of the two PET scans (FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Only one ceCT scan is required to minimise radiation dose. Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained. For the ^{68}Ga-OPS202 PET scan a single low dose CT scan is preferred for the 0.5 and 1.0-hour post dosing acquisitions.** All images **(^{68}Ga-OPS202 PET/CT scans, ^{18}F-FDG-PET/CT scan, and ceCT scan)** will be sent to an imaging core laboratory (ICL) for central blinded reading. **See Section 7 and**

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		...For the study, paraffin embedded slides ~~are~~ required for the evaluation of sstr2 expression by immunohistochemistry staining. Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET ~~imaging~~ at 0.5, 1 and 2 hours after the injection of the IIP. A single ceCT scan will be performed after the 2-hour PET scan, according to the site standard procedure for chest, abdomen, pelvis and brain. ~~A~~ low dose CT may be ~~performed at~~ the 0.5 and~~/or~~ 1 hour PET ~~as well as for~~ the ~~^{18}F-FDG-PET~~ (see the ~~Imaging Review Charter (~~IRC~~)~~). Subjects may be hospitalised overnight upon completion of the ^{68}Ga-OPS202 PET/CT scan at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for a physical examination and laboratory tests.	**the Imaging Review Charter (IRC) for further details.** ...At Screening, after obtaining written informed consent, the investigator will collect all the information required to confirm the subject eligibility including medical and surgical history, physical examination **and vital signs,** laboratory tests (haematology, blood chemistry and urinalysis) and tumour histopathology if available. ...For the study, **the collection of an archived tumour sample (a block is preferred over** paraffin embedded slides**) is** required for the evaluation of sstr2 expression by immunohistochemistry staining. Subjects' eligibility will be re-checked by the investigator at Baseline/Day 1 (Visit 2) before administration of the IIP. If eligibility is re-confirmed, the subject will receive one injection of ^{68}Ga-OPS202 followed by whole body PET**–acquisition** at 0.5, 1 and 2 hours after the injection of the IIP. A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. **This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired with PET scans when necessary for attenuation correction**. Subjects may be hospitalised overnight upon completion of the ^{68}Ga-OPS202 PET/CT scan**s** at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for a physical examination, **vital signs** and laboratory tests. **Also an**

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			^{18}F-FDG-PET scan and ceCT scan will be arranged if not already acquired.
25	3.1 Figure 1	Figure contains strata per invasive stage. Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 evaluable subject scans~~: eight subjects with early disease and eight subjects with advanced disease~~.	Strata removed from figure and footnotes updated. Note: Approximately 54 subjects will be screened to receive IIP to identify 16 sstr2 **positive** evaluable subject scans.
25	3.2	**Primary and Secondary Endpoints and Evaluations** The primary and secondary imaging endpoints will be read by third-party independent readers. ~~Most of the reading will be conducted in a blinded manner by two primary readers and a third to adjudicate any differences.~~ Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain.	**Primary and Secondary Endpoints and Evaluations** The primary and secondary imaging endpoints will be read by third-party independent readers. Co-primary and secondary endpoints will be measured in the primary tumour and key organs consisting of liver, lymph nodes, bone, lungs and brain.
25	3.2.1	**Primary Efficacy Endpoint and Evaluation** • Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202~~)~~.	**Primary Efficacy Endpoint and Evaluation** • Percentage of subjects with sufficiently avid lesion(s) to be identified as a sstr2 positive lesion. (Avid is defined by the blinded readers at one of the **acquisition** timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 **and 1.5-fold or greater uptake than the non-tumoural liver and lung parenchyma)**.
25	3.2.2.1	*Key secondary endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions.	*Key secondary endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. **Significant**

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		• ~~Differences at each of the three timepoints in SUV_{mean} and SUV_{max}, as measured~~ by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain).	**uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.** • **The SUV_{mean} and SUV_{max} in the primary lesions between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed** by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain)**; the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.**
26	3.2.4	**Safety Endpoints and Evaluations** The investigator will report the occurrence of any AE throughout the study~~, including clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis)~~, vital signs (including blood pressure and heart rate) measurements, ~~physical examination findings and body weight measurements~~ at each visit: Screening Visit (Visit 1), Baseline Visit (~~Visit 2; Day 1 and Day 2~~) and End of Study/Early Withdrawal Visit (Visit 3). The electrocardiogram (ECG) findings are to be recorded at the Screening Visit ~~(Visit 1)~~ and the End of Study/Early Withdrawal Visit ~~(Visit 3)~~. Relevant medical history and concomitant	**Safety Endpoints and Evaluations** The investigator will report the occurrence of any AE throughout the study **and** vital signs (including blood pressure and heart rate) measurements at each visit: Screening Visit (Visit 1; **Day -14 to -1**), **Visit 2 (Day 1)**, Baseline Visit **(Visit 2; Day 2)** and End of Study/Early Withdrawal Visit (Visit 3). **Clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis) measurements will be reported at Screening Visit, Baseline Visit and End of Study/Early Withdrawal Visit. Physical examination findings and body weight measurements will be reported at Screening**

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		medications/therapies will also be recorded throughout the study. The following safety endpoints will be evaluated: • Proportion of subjects experiencing at least one AE of any grade according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version ~~4.03~~, including any serious AEs including suspected unexpected serious adverse reactions (SUSARs); all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (as per most recent version)	**Visit, Visit 2 (Day 1) and End of Study/Early Withdrawal Visit.** The electrocardiogram (ECG) findings are to be recorded at the Screening Visit and the End of Study/Early Withdrawal Visit. Relevant medical history and concomitant medications/therapies will also be recorded throughout the study. The following safety endpoints will be evaluated: • Proportion of subjects experiencing at least one AE of any grade according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version **5.0**, including any serious AEs including suspected unexpected serious adverse reactions (SUSARs); all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) (as per most recent version)
27	3.3	**Randomisation and Blinding** This is an open-label non-randomised study. However, independent readers will evaluate ^{68}Ga-OPS202 PET/CT and ^{18}F-FDG-PET images and will be blinded to the acquisition time of the PET scan, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical exam findings. ~~I~~ndependent 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).	**Randomisation and Blinding** This is an open-label non-randomised study. However, **the** independent readers will evaluate ^{68}Ga-OPS202 PET/CT and ^{18}F-FDG-PET/**CT** images and will be blinded to the acquisition time of the PET scan**s and CT scans**, investigator site and clinical status of the subject, including pathology, laboratory, medical history and physical exam findings. **The i**ndependent 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. **Two readers will**

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			read 100% of all the images and third will adjudicate any differences. See the Imaging Review Charter (IRC).
27	3.4	**Maintenance of Randomisation and Blinding** ~~This is an open-label non-randomised study; there is no blinding for the imaging product used. The scan images collected at Visit 2 and ^{18}F-FDG-PET images are to be read centrally in a blinded manner.~~ ~~The images will be sent to a central imaging core laboratory (ICL). The ICL will ensure that the ^{68}Ga-OPS202 PET images and CT images are initially presented to the readers in a blinded manner and randomised to temporal sequence. Blinding includes subject identification, site, type of scanner(s) and acquisition time. Full details of this read will be provided in the IRC.~~	**Maintenance of Randomisation and Blinding** **All blinding is handled by the ICL and described in the IRC.**
28	3.6	**Study Duration** Subject participation in the study will include: • Visit 1: a screening period up to 14 days prior to IIP administration • Visit 2: a single i.v. injection of ~~a fixed activity range of~~ ^{68}Ga-OPS202 on Day 1 followed by PET ~~imaging~~ at 0.5, 1 and 2 hours ±~~5~~ minutes post dosing~~, and a ceCT scan immediately after the 2-hour PET timepoint~~ • Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety.	**Study Duration** Subject participation in the study will include: • Visit 1: a screening period up to 14 days prior to IIP administration • Visit 2: a single i.v. injection **of between 150 MBq to 200 MBq** of ^{68}Ga OPS202 on Day 1 followed by PET **acquisition** at 0.5, 1 and 2 hours ±**10** minutes post dosing. • Visit 3: a follow-up visit at Day 14 (±3 days) for evaluation of safety. • **Within the study an ^{18}F-FDG-PET scan and also a ceCT scan must also be acquired.**
28	3.7	**Stopping Rules and Discontinuation Criteria** ~~There are no formal rules for early termination of this study~~. During the	**Stopping Rules and Discontinuation Criteria** During the conduct of the study, SAEs will be reviewed (see

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		conduct of the study, SAEs will be reviewed (see Section 8.1.3) as they are reported from the study centres to identify safety concerns...	Section 8.1.3) as they are reported from the study centres to identify safety concerns... **Futility Stopping Rule** **If less than three sstr2 positive evaluable subject scans out of 30 consecutive subjects screened with ^{68}Ga-OPS202 PET/CT, or less than 8 out of 50, the study will be stopped.**
31	4.3	**Rationale for Inclusion/Exclusion Criteria** Eligibility criteria include those that define subjects with breast cancer eligible for imaging with ^{68}Ga-OPS202 PET/CT scan.	**Rationale for Inclusion/Exclusion Criteria** Eligibility criteria include those that define subjects with breast cancer eligible for imaging with ^{68}Ga-OPS202 PET/CT scan. **There is no upper limit for age since eligibility criteria exclude conditions that could affect elderly participation in the study.**
32	5.1 Table 2	Visit 2 has only one column (Day 1). Physical examination, Haematology, Blood chemistry and Urinalysis were removed from Day 1 column. (f) **Physical examination**: Major body systems, body weight, height (screening visit only)~~, vital signs 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate).~~ ~~(g)~~... ~~(h)~~... ~~(i)~~ **Blood chemistry:** urea, creatinine, chloride, bicarbonate, sodium, potassium, calcium, phosphate, total bilirubin, conjugated bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose. ~~(J)~~...	Visit 2 has additional column for Day 2, which include: Concomitant therapies, Vital signs, Haematology, Blood chemistry, Urinalysis and Adverse events. Added physical examination at Visit 2 Day 1. New row: **Contrast enhanced CT [m]With ^{68}Ga-OPS202 PET or ^{18}F-FDG-PET** (f) **Physical examination**: Major body systems, body weight, height (screening visit only). **(g) Vital signs**: 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure **and** heart rate, body temperature, respiratory rate). **(h)...** **(i)...** **(J) Blood chemistry:** urea, creatinine, **creatinine clearance,** chloride, bicarbonate, sodium, potassium, calcium, phosphate,

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		~~(k)~~... (l) **^{68}Ga-OPS202 PET/CT imaging**: PET ~~imaging~~ at 0.5, 1 and 2 hours after ^{68}Ga-OPS202 administration. ~~Anonymised images to be sent to the Imaging Core Lab.~~ Iodinated i.v. CT contrast imaging (chest, abdomen, pelvis and brain) after the 2 hour PET scan. ~~A low dose CT may be performed at the 0.5 and/or 1 hour PET~~ (see the Imaging Review Charter (IRC)). ~~(m)~~ **^{18}F-FDG-PET scan**: ^{18}F-FDG-PET scan~~s~~, which is part of routine clinical diagnosis, will be performed during the study period ~~(including the Screening period before Day 1),~~ and images sent to ICL. A low dose CT may be performed with the ^{18}F-FDG-PET (see the ~~Imaging Review Charter (~~IRC~~)~~) ~~(n)~~... ~~(o)~~... ~~(p)~~ **Biopsy:** To be performed if not already done. Tumour biopsy, which is not a prerequisite for inclusion, is routinely performed for confirmation and staging of the disease, as well as classification according to hormone receptor status and HER2 status. For the study, paraffin embedded slides ~~are~~ required for the evaluation of sstr2 expression by immunohistochemistry staining.	total bilirubin, conjugated bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, albumin, total protein, total cholesterol, triglycerides, fasting glucose. **(k)...** **(l)...** **(m) ^{68}Ga-OPS202 PET/CT imaging**: PET **acquisition** at 0.5, 1 and 2 hours after ^{68}Ga-OPS202 administration. Iodinated i.v. CT contrast imaging (chest, abdomen, pelvis and brain). **A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired for the other PET scans when the ceCT is not obtained** (see the Imaging Review Charter (IRC)). **Anonymised and blinded to acquisition time images will be sent to the ICL**. **(n) ^{18}F-FDG-PET scan**: ^{18}F-FDG-PET scan, which is part of routine clinical diagnosis, will be performed during the study period and images sent to ICL. A **ceCT or a** low dose CT may be performed with the ^{18}F-FDG-PET (see the IRC) **(o)**... **(p)**... (**q**) **Biopsy:** To be performed if not already done. Tumour biopsy, which is not a prerequisite for inclusion, is routinely performed for confirmation and staging of the disease, as well as classification according to hormone receptor status and HER2 status. For the study, **an archived tumour sample (block is preferred** paraffin embedded slides**) is**

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			required for the evaluation of sstr2 expression by immunohistochemistry staining.
34	5.2.1	***Procedures for Screening and Enrolment (Visit 1)*** ... • Collection of historical paraffin embedded breast tumour slides ~~(if available)~~ • ^{18}F-FDG-PET (which can also be performed at any time during the study period, including the Screening period).	***Procedures for Screening and Enrolment (Visit 1)*** ... • Collection of historical paraffin embedded breast tumour **blocks or** slides **with anatomical location of the lesion(s) indicated** • ^{18}F-FDG-PET **scan** (which can also be performed at any time during the study period, including the Screening period).
34	5.2.2	**Procedures Before Study IIP Administration (Day 1, Visit 2 Pre-dose)** The following procedures will be performed on Day 1, prior to the IIP administration: • Eligibility check (inclusion/exclusion criteria) • Pregnancy test (urine) • Concomitant therapies • Review of AEs.	**Procedures Before Study IIP Administration (Day 1, Visit 2 Pre-dose)** The following procedures will be performed on Day 1, prior to the IIP administration: • Eligibility check (inclusion/exclusion criteria) **• Vital signs (body temperature, supine and standing blood pressure, heart rate and respiratory rate)** **• Physical examination (including body weight)** • Pregnancy test (urine) • Concomitant therapies • Review of AEs.
34	5.2.4	**Procedures after IIP Administration (Day 1 and Day 2, Visit 2 Post-dose)** ... • A contrast-enhanced CT scan performed after the 2-hour PET scan, according to the procedure for chest, abdomen, pelvis and brain defined in the Imaging Manual. ... The following procedures will be performed at Visit 2 Day 2:	**Procedures after IIP Administration (Day 1 and Day 2, Visit 2 Post-dose)** ... • **A single ceCT scan will be performed according to the site standard procedure for chest, abdomen, pelvis and brain. This can be acquired after either of the two PET scans (^{18}F-FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired**

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		... ~~• Physical examination~~	**with PET scans when necessary for attenuation correction. See IRC for further details.**
35	5.2.5	**End of Study Visit or Early Withdrawal Visit (Day 14±3, Visit 3)** ... • Physical examination	**End of Study Visit or Early Withdrawal Visit (Day 14±3, Visit 3)** ... • Physical examination **including body weight**
35	6	**~~IMAGING~~ OF SUBJECTS**	**INVESTIGATIONAL IMAGING PRODUCT AND DOSING OF SUBJECTS**
36	6.1.1.1		New subsection *6.1.1.1 Spillage* All due precautions and site procedures should be implemented to prevent spillage or leakage of radiodiagnostics. Syringes, intravenous lines, venous access should all be secured and the connections thoroughly checked. The injection/infusion line should be taped in a loop and taped to the subject to prevent direct tension between the line and the venous access. Despite precautions, if spillage or leakage should occur, then the site procedures must be implemented to protect the subject, staff and members of the public from radiation exposure. The subject should be moved from the area of the spillage or leakage while the area is decontaminated. Details of the spillage or leakage should be recorded (including how the incident happened, the time of the incident, an estimate (if possible) of the amount of substance lost) and the measures taken. In addition, the incident is to be reported in the same manner as an adverse event using the MedDRA PT Product Leakage and as appropriate PT Occupational

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			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).
37	6.1.4	**Investigational Imaging Product (^{68}Ga-OPS202)** ... • Radiolabelling of the precursor OPS202 achieved by the addition of a ~~5~~ mL sterile hydrochloric acid solution of ^{68}Ga, eluted from a sterile pharmaceutical grade ^{68}Ge/^{68}Ga generator. ... The 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 dose injected to subject.	**Investigational Imaging Product (^{68}Ga-OPS202)** ... • Radiolabelling of the precursor OPS202 achieved by the addition of a **6**-mL sterile hydrochloric acid solution of ^{68}Ga, eluted from a sterile pharmaceutical grade ^{68}Ge/^{68}Ga generator. ... 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 dose injected to subject. **In addition, any extravasation during infusion should be measured and this radioactivity deducted from the calculated amount injected into the subject.**
37	6.2	**Study Drugs Administered** ~~At Screening, subjects will be allocated a subject number. Following confirmation of eligibility for the study at Visit 2, subjects will receive a single dose of ^{68}Ga-OPS202 (IIP), consisting of a peptide mass up to 45 µg, with a radioactivity range of 150-200 MBq activity of ^{68}Ga.~~ ^{68}Ga-OPS202 is prepared, up to 3 hours prior to administration, by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit containing 50 µg of peptide.	**Study Drugs Administered** ^{68}Ga-OPS202 is prepared, up to 3 hours prior to administration, by ^{68}Ga-radiolabelling of an OPS202 radiolabelling kit containing 50 µg of peptide.
38	7	**ASSESSMENT OF EFFICACY** For the primary, secondary and exploratory endpoints all the sets of images obtained at Visit 2 and one	**ASSESSMENT OF EFFICACY** For the primary, secondary and exploratory endpoints all the sets of images obtained at Visit 2 and

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		^{18}F-FDG-PET will be sent to an ICL for quality control and management of the reads. The centralised reads will be undertaken by two independent experienced radiologists and/or nuclear medicine physicians, and a third for adjudication of discordances. The readers will be specifically trained for this protocol. Full details of the read design and conduct will be provided in the IRC. For the primary endpoint analysis, the number of lesions ~~on each subject scan will be counted at each of the three timepoints~~. Scans will be blinded to subject identification, site and timing post injection. ~~In case of discrepancy, images will go to the adjudicator (third reader) for a final read and adjudication.~~ ~~After blinded reading, the readers will compare the three scans (the three acquisitions of ^{68}Ga-OPS202) contemporaneously for each subject and note which image(s), if any, provides superior images based on overall image quality and lesion count.~~ ... (1) Review of the three image sets of ^{68}Ga-OPS202 scans in randomised fashion~~, without and~~ with CT image fusion. The ceCT images acquired on the same day will be used for co-registration (2) ^{18}F-FDG-PET images for standard-of-truth assessments will be reviewed by two radiologists not involved in ^{68}Ga-OPS202 PET/CT images read, and the lesions mapped to the ^{68}Ga-OPS202 read. ... (5) For image quality, direct comparison of the three ^{68}Ga-OPS202 scans acquired at different times, will be conducted for the primary breast cancer and then for all other lesions as the final step of the blinded read. The	one ^{18}F-FDG-PET **and one ceCT scan** will be sent to an ICL for quality control and management of the reads. The centralised reads will be undertaken by two independent experienced radiologists and/or nuclear medicine physicians, and a third for adjudication of discordances **for most of the reads**. The readers will be specifically trained for this protocol. Full details of the read design and conduct will be provided in the IRC. For the primary endpoint analysis, the number of lesions **and quality of the images will be taken into consideration by the readers.** Scans will be blinded to subject identification, site and timing post injection. **No adjudication will be conducted as inter-reader differences will be part of the evaluation.** … (1) Review of the three image sets of ^{68}Ga-OPS202 scans in randomised fashion, with CT image fusion. The ceCT images acquired will be used for co-registration. **Two readers will read and a third will adjudicate any differences.** (2) ^{18}F-FDG-PET images for standard-of-truth assessments will be reviewed by two radiologists not involved in ^{68}Ga-OPS202 PET/CT images read, and the lesions mapped to the ^{68}Ga-OPS202 read. **Two readers will read and a third will adjudicate any differences.** … (5) For image quality, direct comparison of the three ^{68}Ga-OPS202 scans acquired at different times, will be conducted for the primary breast cancer and then for

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		readers will be allowed to select whether one, two or all three acquisitions are optimal. The readers will be blinded to time point sequence. (6) The ^{68}Ga-OPS202 PET scan~~s~~ will be compared with the ^{18}F-FDG-PET scan~~s~~ (with ceCT). ~~(A ceCT scan will be acquired for use with the ^{68}Ga-OPS202 PET and ^{18}F-FDG-PET scan. This ceCT scan can be acquired with either PET scan as long as they are obtained within a 2-week timeframe. A second ceCT scan will be acquired if the PET scans are greater than 2 weeks apart. When a PET scan is obtained without a ceCT scan, a low dose CT scan will be obtained for attenuation correction, according to site standard practice.)~~ ... (2) The identification of the optimum acquisition times based on differences in the number of lesions identified at each scan, and the reader interpretation of the optimum image in the primary breast lesions. The optimum image acquisition time could be one, two or all three acquisitions i.e. .no noticeable difference between 0.5, 1 and 2 hours post infusion.	all other lesions as the final step of the blinded read. The readers will be allowed to select whether one, two or all three acquisitions are optimal. The readers will be blinded to time point sequence. **No adjudication will be required.** (6) The ^{68}Ga-OPS202 PET scan will be compared with the ^{18}F-FDG-PET scan (with ceCT). … (2) The identification of the optimum acquisition time**(s)** based on differences in the number of lesions identified at each scan, and the reader interpretation of the optimum image in the primary breast lesions. The optimum image acquisition time could be one, two or all three acquisitions **timepoints** i.e. .no noticeable difference between 0.5, 1 and 2 hours post infusion.
39	7	*Key Secondary Endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. ... *Other Secondary Endpoints:* • Comparison to standard-of-truth for the primary breast tumour: - (^{68}Ga-OPS202 PET/CT) / (^{18}F-FDG-PET) ...	*Key Secondary Endpoint:* • Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours), and reader interpretation of optimal image(s) in nodular and metastatic lesions. **Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and**

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		Exploratory Endpoints: • Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging sstr2 positive breast cancer ~~tumors~~ by both subject based and lesion-based analysis compared to standard-of-truth	**1.5-fold greater uptake than in the non-tumoural liver and lung parenchyma.** ... *Other Secondary Endpoints:* • Comparison to standard-of-truth for the primary breast tumour: - (^{68}Ga-OPS202 PET/CT) / (^{18}F-FDG-PET/**CT**) ... *Exploratory Endpoints:* • Preliminary diagnostic sensitivity of ^{68}Ga-OPS202 imaging sstr2 positive breast cancer **tumours** by both subject based and lesion-based analysis compared to standard-of-truth
40	7	**(c) Methods and Timing of Assessing, Recording, and Analysing Efficacy Data** ... • All ^{68}Ga-OPS202 PET/CT scans • One ^{18}F-FDG-PET/CT scan. •One CeCT scan. The details of imaging ~~set~~ management and read design will be fully described in the IRC. This will include the following:	**(c) Methods and Timing of Assessing, Recording, and Analysing Efficacy Data** ... • All ^{68}Ga-OPS202 PET/CT scans • One ^{18}F-FDG-PET/**CT** scan. **•One ceCT scan.** The details of **the** imaging management and read design will be fully described in the IRC. This will include the following:
40	7.1	**Eligible and Evaluable Subjects** - At least two ^{68}Ga-OPS202 PET scans that are readable (three images are to be acquired but 2 of these MUST be readable by the central readers. If only two PET scans are acquired BOTH must be readable) with at least one avid lesion identified by central readers.	**Eligible and Evaluable Subjects** - At least two ^{68}Ga-OPS202 PET scans that are readable (three images are to be acquired but 2 of these**,** MUST be readable by the central readers**; if** only two PET scans are acquired BOTH must be readable) with at least one avid lesion identified by central readers.
41	8.1.1.1	*Intensity Classification* Adverse events will be recorded and graded according to the current	*Intensity Classification* Adverse events will be recorded and graded according to the

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		version of the NCI CTCAE (version ~~4.03~~).	current version of the NCI-CTCAE (version **5.0**).
43-44	8.1.3	Any SAE must be reported immediately (within 24 hours), ~~using the email~~ 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 SAE must be reported immediately (within 24 hours), **to Ipsen Pharmacovigilance email (preferably) or fax number** specified at the beginning of this protocol, independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.
45	8.2	**Clinical Laboratory Tests** Blood samples will be collected at all study visits (Screening Visit [Visit 1], ~~Baseline/Day 1 [Visit 2],~~ Day 2 [Visit 2], and End of Study/Early Withdrawal [Visit 3]) (see schedule of assessment in Table 2) for the evaluation of haematology and serum chemistry.	**Clinical Laboratory Tests** Blood samples will be collected at all study visits (Screening Visit [Visit 1], Day 2 [Visit 2], and End of Study/Early Withdrawal [Visit 3]) (see schedule of assessment in Table 2) for the evaluation of haematology and serum chemistry.
46	8.2.2	**Blood Biochemistry** Blood samples will be collected at all visits to assess the following parameters: • urea, creatinine, total bilirubin, conjugated bilirubin	**Blood Biochemistry** Blood samples will be collected at all visits to assess the following parameters: • urea, creatinine, **creatinine clearance,** total bilirubin, conjugated bilirubin
46	8.3	**Physical Examination** Physical examinations, including body weight, will be conducted at Screening (Visit 1), IIP administration visit (Visit 2 only on Day ~~2),~~ and End of Study (Visit 3)/Early Withdrawal (see Table 2), and height will be measured at Screening.	**Physical Examination** Physical examinations, including body weight, will be conducted at Screening (Visit 1), IIP administration visit (Visit 2 only on Day **1**), and End of Study (Visit 3)/Early Withdrawal (see Table 2), and height will be measured at Screening.
51	11.1	**Analyses Populations** ... • **Sstr2 positive population:** All subjects who received the dose of study IIP and for whom ^{68}Ga-OPS202 PET/CT scan images are readable for at least one timepoint and one avid lesion ~~was~~ identified by central readers.	**Analyses Populations** ... • **Sstr2 positive population:** All subjects who received the dose of study IIP and for whom ^{68}Ga-OPS202 PET/CT scan images are readable for at least one timepoint and **have** one avid lesion identified by central

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		• Sstr2 positive evaluable population: ^{68}Ga-OPS202 sstr2 positive population with at least two evaluable ~~timepoints and~~ ^{68}Ga-OPS202 timepoints, ^{18}F-FDG-PET F-FDG-PET scan ~~identified~~ by the central readers.	readers **^{18}F-FDG-PET/CT scan and a ceCT scan confirmed by the central readers** • Sstr2 positive evaluable population: ^{68}Ga-OPS202 sstr2 positive population with at least two evaluable **^{68}Ga-OPS202 timepoints**, ^{18}F-FDG-PET/**CT** scan **and a ceCT scan confirmed** by the central readers.
49	11.2	**Sample Size Determination** It is anticipated that a total of 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 ~~screening~~, to obtain around 16 sstr2 evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be ~~screened with~~ ^{68}Ga-OPS202 in the study will be ~~approximately 54~~. However, when the ICL identifies 16 sstr2 evaluable subjects, with ~~eight~~ subjects having ~~early disease and eight subjects~~ advanced disease, the study will be complete. This estimation of 16 sstr2 positive evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited as a replacement to ensure an adequate sample size in the sstr2 positive evaluable set.	**Sample Size Determination** It is anticipated that a total of **approximately** 54 subjects will be enrolled in the study for ^{68}Ga-OPS202 **PET/CT imaging**, to obtain around 16 sstr2 **positive BC** evaluable subjects. Considering the estimated prevalence of sstr2 overexpression in breast cancer, the overall number of subjects to be a**dministered** ^{68}Ga-OPS202 in the study will be **over 50**. However, when the ICL identifies 16 sstr2 **positive** evaluable subjects, with **a minimum of two** subjects **with** advanced disease, the study will be complete. This estimation of 16 sstr2 positive **BC** evaluable subjects is considered appropriate for a descriptive analysis and it is not based on a formal statistical sample size calculation. In the event that a subject misses an imaging exam and/or measurement relevant to the primary and key secondary endpoints, an additional subject will be recruited as a replacement to ensure an adequate sample size in the sstr2 positive **BC** evaluable set.
50-51	11.4.4	***Efficacy Evaluation*** *Key Secondary Endpoint:*	***Efficacy Evaluation*** *Key Secondary Endpoint:*

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		• Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours) and reader interpretation of optimal image(s) in nodular and metastatic lesions. ~~• Differences at each of the three timepoints in SUV_{mean} and SUV_{max}, as measured by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain).~~ *Other Secondary Endpoints:* • Differences in relative lesion counts as a ratio of the number of lesions detected by ^{68}Ga-OPS202 at 0.5, 1 and 2 hours post dose respectively, compared to the number of lesions assessed by standard-of-truth (descriptive analyses). The standard-of-truth is the ^{18}F-FDG PET scan images acquired at any time during the study period (including the Screening period)...	• •Differences in the number of lesions detected by ^{68}Ga-OPS202 between the three PET acquisition timepoints (0.5, 1 and 2 hours) and reader interpretation of optimal image(s) in nodular and metastatic lesions. **Significant uptake of ^{68}Ga-OPS202 for the evaluation of a lesion is an avid lesion defined by the blinded readers at one of the acquisition timepoints as an easily identifiable lesion radiologically, where there has been clear focal uptake of ^{68}Ga-OPS202 and 1.5-fold or greater uptake than in the non-tumoural liver and lung parenchyma.** • **The SUV_{mean} and SUV_{max} in the primary lesion between each of the three timepoints, measured in the most avid lesions (using the ^{68}Ga-OPS202 scans). This is assessed by the tumour-to-background ratio in the primary tumour and each of the major anatomic sites (liver, lymph nodes, bone, lungs and brain); the background consists of non-tumoural liver parenchyma or aortic blood where sufficient liver is not available. Identification of lesions to be used will be made by one of the two primary readers.** *Other Secondary Endpoints:* • Differences in relative lesion counts as a ratio of the number of lesions detected by ^{68}Ga-OPS202/**ceCT** at 0.5, 1 and 2

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			hours post dose respectively, compared to the number of lesions assessed by standard-of-truth (descriptive analyses). The standard-of-truth is the ^{18}F-FDG-PET/**CT** scan images acquired at any time during the study period (including the Screening period)…
51	11.4.6	*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 ~~4.03~~) will be coded using MedDRA dictionary (latest available version).	*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).

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-01070-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 2.0, Amendment 1.0; 27 June 2018**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASONS FOR CHANGES	The protocol was amended to modify the restrictions on the minimum number of subjects per tumour stage, to update the version of the NCI CTCAE version to be used, to update pharmacovigilance contact details, to add instructions on spillage of the product, to make clarifications and to correct typographical errors.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 2 Protocol Summary of Changes - Amendment 2.0

STUDY NUMBER	D-FR-01070-003
PROTOCOL TITLE:	A non-randomised phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 3.0, Amendment 2.0; 14 September 2018

THE FOLLOWING AMENDMENTS ARE PROPOSED:

Version Date		**27 JUNE 2018**	**14 SEPTEMBER 2018**
Page	**Section**	**WAS**	**IS**
1	Title page	Version 2.0, Amendment 1.0; 27 June 2018	Version 3.0, Amendment 2.0; 14 September 2018
8	Synopsis	*Exclusion criteria:* ... 15. Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus~~)~~, and/or subjects treated with curative intent and free from disease for more than 5 years.	*Exclusion criteria:* ... 15. Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus, and/or subjects treated with curative intent and free from disease for more than 5 years**)**.
31	4.2	**Exclusion Criteria** ... (15) Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus~~)~~, and/or subjects treated with curative intent and free from disease for more than 5 years.	**Exclusion Criteria** ... (15) Subject who experienced a previous cancer (except basocellular carcinoma of the skin and/or in situ carcinoma of the cervix/uterus, and/or subjects treated with curative intent and free from disease for more than 5 years**)**.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-01070-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 3.0, Amendment 2.0; 14 September 2018**	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASONS FOR CHANGES	The protocol was amended to correct a typo in exclusion criterion 15, which defines previous cancer of subjects not eligible for the study.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 3 Protocol Summary of Changes - Amendment 3.0

STUDY NUMBER	D-FR-01070-003
PROTOCOL TITLE:	A non-randomised phase II study to evaluate the optimal uptake time of ^{68}Ga-OPS202 as a sstr2 positive PET imaging agent in subjects with newly diagnosed breast cancer
AMENDED PROTOCOL VERSION NUMBER & DATE	Version 4.0, Amendment 3.0; 20 May 2019

THE FOLLOWING AMENDMENTS ARE PROPOSED:

Version Date		**14 SEPTEMBER 2018**	**20 MAY 2019**
Page	**Section**	**WAS**	**IS**
1	Title page	Version 3.0, Amendment 2.0; 14 September 2018	Version **4.0**, Amendment **3.0**; **20 May 2019**
1	Title page	**Sponsor ~~Signatory~~:** PPD Ipsen ~~Innovation Global Drug Development~~ ~~ZI de Courtaboeuf 5, Avenue du Canada~~ ~~91940 Les Ulis, France~~ ~~Tel:~~ PPD ~~(mobile:~~ PPD ~~Fax:~~ PPD	**Sponsor's Medically Responsible Person:** PPD **Ipsen Pharma** **Global Drug Development** **65 quai Georges Gorse** **92100 Boulogne-Billancourt** **France** **Mobile:** PPD
2	INVESTIGATOR'S AGREEMENT	**Sponsor's Representative Signature:** NAME: PPD TITLE: PPD SIGNATURE: DATE: OFFICE: Ipsen ~~Innovation Global Drug Development~~ ~~Z.I. de Courtaboeuf~~ ~~5 avenue du Canada~~ ~~91940 Les Ulis~~ ~~France~~	**Sponsor's Representative Signature:** NAME: PPD TITLE: PPD **Ipsen Biopharm Ltd** SIGNATURE: DATE: OFFICE: Ipsen **Biopharm Ltd** **102 Park Drive** **Milton Park** **Abingdon, OX14 4RY** **United Kingdom**

Version Date		14 SEPTEMBER 2018	20 MAY 2019
Page	**Section**	**WAS**	**IS**
4	SUMMARY OF CHANGES		New Section: **SUMMARY OF CHANGES** **The current version of the protocol was released on 20 May 2019 and includes Amendment 3. For all protocol amendments, amendment forms were prepared and are provided in the Appendices listed in Table 1. All modifications (except minor changes) are presented in the appendices.** **Table 1 List of Protocol Amendments** **Amendment Release date Amendment form** **1 27 June 2018 Appendix 1** **2 14 September 2018 Appendix 2** **3 20 May 2019 Appendix 3**
5	Synopsis	**Name of finished product:** ~~^{68}Ga-OPS202 solution for injection.~~ **Name of active ingredient(s):** ^{68}Ga-OPS202 **Planned study period:** FPI: July 2018 - LPO: December ~~2018~~	**Name of finished product: ^{68}Ga-OPS202 - ^{68}Ga-satoreotide trizoxetan** **Name of active ingredient(s):** ^{68}Ga-OPS202 - **INN for OPS202 is satoreotide trizoxetan** **Planned study period:** FPI: July 2018 - LPO: December **2018**
19	LIST OF ABBREVIATIONS		**Added:** **INN International nonproprietary name**
21	1.2	**Name and Description of Investigational Imaging Product** OPS202 is a new generation somatostatin analogue (antagonist) compound with potential superior tumour detection	**Name and Description of Investigational Imaging Product** OPS202 **(satoreotide trizoxetan)** is a new generation somatostatin analogue (antagonist) compound with potential superior tumour detection

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Page	**Section**	**WAS**	**IS**
23	1.6	**Population to Be Studied** Several types of tumours other than NETs express sstr2 making the imaging of these tumours with peptide receptor radionuclide such as 68Ga-OPS202 possible. This study will enrol adult female subjects with newly diagnosed early or locally advanced breast cancer to detect those expressing sstr2.	**Population to Be Studied** Several types of tumours other than NETs express sstr2 making the imaging of these tumours with peptide receptor radionuclide such as 68Ga-OPS202 possible. This study will enrol adult female subjects with newly diagnosed early or advanced breast cancer to detect those expressing sstr2.
25	3.1	**General Design and Study Schema** ... Subjects may be hospitalised overnight upon completion of the ^{68}Ga-OPS202 PET/CT scans at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for ~~a physical examination,~~ vital signs and laboratory tests.	**General Design and Study Schema** ... Subjects may be hospitalised overnight upon completion of the 68Ga-OPS202 PET/CT scans at the discretion of the investigator. All subjects (either hospitalised or not) will attend a consultation on Day 2 for vital signs and laboratory tests.
27	3.2.4	**Safety Endpoints and Evaluations** The investigator will report the occurrence of any AE throughout the study and vital signs (including blood pressure and heart rate) measurements at each visit: Screening Visit (Visit 1; Day -14 to -1), Visit 2 (Day 1), ~~Baseline Visit (~~Visit 2~~;~~ Day 2) and End of Study/Early Withdrawal Visit (Visit 3). Clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis) measurements will be reported at Screening Visit, ~~Baseline~~ Visit and End of Study/Early Withdrawal Visit.	**Safety Endpoints and Evaluations** The investigator will report the occurrence of any AE throughout the study and vital signs (including blood pressure and heart rate) measurements at each visit: Screening Visit (Visit 1; Day -14 to -1), Visit 2 (Day 1), Visit 2 **(**Day 2) and End of Study/Early Withdrawal Visit (Visit 3). Clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis) measurements will be reported at Screening Visit, Visit **2 (Day 2)** and End of Study/Early Withdrawal Visit.
29	3.5	**Study Imaging Product and Dosage** **...**	**Study Imaging Product and Dosage** **...**

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		The radiolabelling kit will be packaged ~~by Beaufour Ipsen Industrie, 20 rue Ethe Virton 28100 Dreux, France~~ and delivered in a sufficient quantity to the investigational sites with a delivery note including an acknowledgement of receipt.	The radiolabelling kit will be packaged and delivered in a sufficient quantity to the investigational sites with a delivery note including an acknowledgement of receipt.
33	5.1	**Study Schedule** Footnotes: (a) Study visits: Screening Visit up to 14 days before IIP administration; Subjects may be hospitalised overnight at the discretion of the investigator at Visit 2. All subjects (either hospitalised or not) will attend consultation on Day 2, which is part of Visit 2, for: review of AEs, new or changed concomitant medications, vital signs, physical examination, haematology, biochemistry, urinalysis. ... (g) **Vital signs:** 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure and heart rate, body temperature, respiratory rate). ... (i) **Haematology:** Red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils~~, and others~~) and platelet count.	**Study Schedule** Footnotes: (a) Study visits: Screening Visit up to 14 days before IIP administration; Subjects may be hospitalised overnight at the discretion of the investigator at Visit 2. All subjects (either hospitalised or not) will attend consultation on Day 2, which is part of Visit 2, for: review of AEs, new or changed concomitant medications, vital signs, haematology, biochemistry, urinalysis. ... (g) **Vital signs: pre-dose and at** 0.5, 1, 2 and 4 hours post-injection (supine and standing systolic and diastolic blood pressure and heart rate, body temperature, respiratory rate). ... (i) **Haematology:** Red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.
38	6.3	**Concomitant Medication/ Therapy**	**Concomitant Medication/ Therapy**

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		... The following concomitant medications /therapies are not permitted during this study up to 48 hours post PET/CT scan: • Administration of ~~a~~ radiopharmaceutical ~~within 8 half-lives of its radionuclide~~	... The following concomitant medications /therapies are not permitted during this study up to 48 hours post PET/CT scan: • Administration of **any** radiopharmaceutical
38	6.4	**Procedures for Monitoring Subject Compliance** ...The injected peptide mass dose and radioactivity dose will be recorded in the medical file and in the eCRF for each subject.	**Procedures for Monitoring Subject Compliance** ...The injected peptide mass dose and radioactivity dose **(calculated from the IIP volume)** will be recorded in the medical file and in the eCRF for each subject.
43	8.1.1.4	*Laboratory Test Abnormalities* ... • They are considered as clinically significant by the investigator~~.~~	*Laboratory Test Abnormalities* ... • They are considered as clinically significant by the investigator**, or the laboratory test abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline based on sponsor review**.
46	8.2.1	***Haematology*** ... white blood cell (WBC) absolute count (neutrophils, lymphocytes, monocytes, eosinophils, basophils~~, and others~~) and platelet count.	***Haematology*** ... white blood cell (WBC) absolute count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.
47	8.4	**Vital Signs** Blood pressure and heart rate will be assessed at Screening (Visit 1), IIP administration visit (Visit 2 Day 1 at 0.5, 1, 2, 4 hours post-injection and on Day 2)...	**Vital Signs** Blood pressure and heart rate will be assessed at Screening (Visit 1), IIP administration visit (Visit 2**:** Day 1 **pre-dose and** at 0.5, 1, 2, 4 hours post-injection and on Day 2)...

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	D-FR-01070-003		
AMENDED PROTOCOL VERSION NUMBER & DATE	**Version 4.0, Amendment 3.0; 20 May 2019**		
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒		
REASONS FOR CHANGES	The protocol was amended to update personnel (Sponsor's representative and medically responsible person), to amend concomitant medications that are not allowed and conditions in which abnormalities in laboratory test values should be reported as AEs, to make minor corrections and clarifications.		
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*	
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*	
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*	
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*	