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STATISTICAL AND ANALYSIS PLAN

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

PROTOCOL VERSION AND DATE: 3.0 – 14 SEPTEMBER 2018

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EUDRACT NUMBER	2018-000028-33
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.
SAP VERSION:	Final Version 2.0
SAP DATE:	10 January 2020

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

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

History of Changes				
Old Version Number		Date Old Version	Date New Version	Primary Reason for Change
Page	Section	Was	Is	
		30 Aug 2018	10 Jan 2020	- Update in approval page - CRO name: Removal of [redacted] - Statement of decision of study premature termination - Section 3.2: Deletion of planned analyses and/or outputs.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

- **ßHCG** Beta human chorionic gonadotropin
- **AE:** Adverse Event
- **ALT:** Alanine aminotransferase
- **AP:** Alkaline phosphatase
- **AST:** Aspartate aminotransferase
- **ATC:** Anatomical Therapeutic Chemical
- **BC:** Breast cancer
- **BMI:** Body mass index
- **BUN:** Blood urea nitrogen
- **ceCT** Contrast enhanced CT
- **CI:** Confidence Interval
- **CRO:** Contract research organisation
- **CT:** Computed tomography
- **D:** Day
- **e:** Electronic
- **ECG:** Electrocardiogram
- **ECOG:** Eastern Cooperative Oncology Group
- **eCRF:** Electronic case report form
- **EDC:** Electronic data capture
- **EOS:** End Of Study
- **EW:** Early Withdrawal
- **18F-FDG:** ^{18}F-fluorodeoxyglucose
- **68Ga:** Gallium - 68
- **GCP:** Good Clinical Practice
- **GGT:** Gamma-Glutamyl Transferase
- **HCG:** Human chorionic gonadotropin
- **i.v.:** Intravenous
- **ICH:** International Conference on Harmonisation
- **ICL:** Imaging core laboratory
- **IIP:** Investigational Imaging Product
- **IRC:** Imaging review charter

- **LLN:** Lower limit of normal range
- **max:** Maximum
- **MBq:** Megabecquerel
- **MCH:** Mean corpuscular haemoglobin
- **MCHC:** Mean corpuscular haemoglobin concentration
- **MCV:** Mean corpuscular volume
- **MedDRA:** Medical Dictionary for Regulatory Activities
- **min:** Minimum
- **NCI-CTCAE:** National Cancer Institute - Common Terminology Criteria for Adverse Events
- **PET:** Positron emission tomography
- **PT:** Preferred Term
- **QC:** Quality control
- **QRS:** QRS interval duration
- **QT:** Time interval for ventricular depolarisation and repolarisation
- **QTc:** Corrected QT interval
- **RBC:** Red blood cell
- **SAE:** Serious Adverse Event
- **SAP:** Statistical and Analysis Plan
- **SAS®:** Statistical Analysis System®
- **SD:** Standard deviation
- **SI:** Standard International
- **SNR:** Signal-to-noise ratio
- **SOC:** System organ class
- **SOP:** Standard Operating Procedure
- **SOT:** Standard-of-truth
- **SSA:** Somatostatin analogues
- **sstr:** Somatostatin receptors
- **sstr2:** Somatostatin receptor subtype 2
- **SUSAR:** Suspected unexpected serious adverse reaction
- **SUV:** Standardised uptake value
- **SUV_{max}:** Maximum standardized uptake value

- **SUV_{mean}:** Mean standardized uptake value
- **TEAE:** Treatment Emergent Adverse Event
- **TFLs:** Tables, Figures and Listings
- **TNM:** Tumour, node and metastasis
- **ULN:** Upper limit of normal range
- **V:** Volume of distribution
- **VOI:** Volume of interest
- **WBC:** White blood cell
- **WHO:** World Health Organization
- **WHO-DD:** World Health Organization (WHO) Drug Dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

The co-primary objectives of the study are to evaluate the percentage of women with newly diagnosed breast cancer who have somatostatin receptor 2 (sstr2) positive lesions that are identified using ^{68}Ga-OPS202 and to define the optimal positron emission tomography (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.

1.1.2 Secondary objectives

The secondary objectives of the study are as follows:

- 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.

1.1.3 Exploratory objectives

The exploratory objectives of the study include the following:

- To provide preliminary estimates of the sensitivity of ^{68}Ga-OPS202 PET/computed tomography (CT) scan imaging, as well as SUV ratio 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.

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 approximately 1.5-fold uptake than the non-tumoural liver and lung parenchyma.

1.2 Study design

This is a non-randomised, open-label, 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.

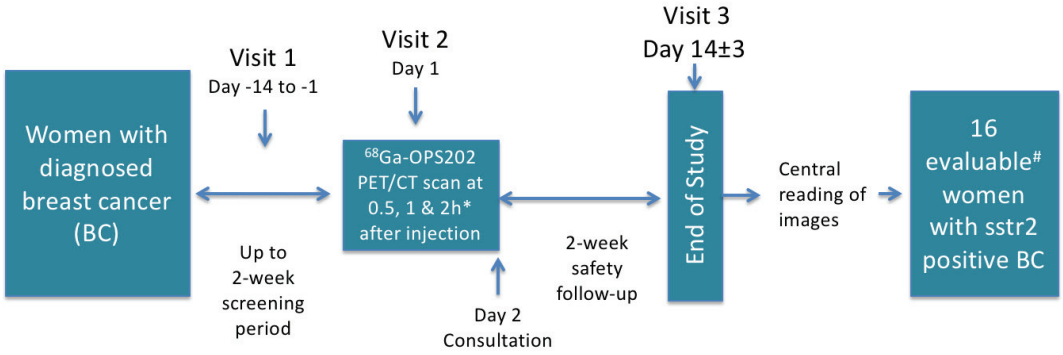
A single contrast enhanced computed tomography (ceCT) scan is required for the study. This can be acquired after either of the two PET scans (^{18}FDG-PET or ^{68}Ga OPS202 post the 2-hour acquisition). Thus, only one ceCT scan is required to minimize radiation dose. Low-dose CT scans will be acquired for the other PET scans where 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 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.

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.

1.2.1 Study population

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

Adults female subjects with newly diagnosed (early or advanced) breast cancer and Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less will be recruited in this study.

1.2.2 Study exposure

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

- Visit 1: A screening period up to 14 days prior to IIP administration
- Visit 2, Day 1: A single i.v. injection of between 150 MBq to 200 MBq of ^{68}Ga-OPS202 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.

At the end of Visit 3, the subject's participation in the study will end.

Overall duration of entire study, estimated as the time from set-up to close-out and reporting, will be approximately 20 months.

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.

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

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

This is a non-randomised, single-arm phase II clinical study. 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.

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.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

For the primary, secondary and exploratory endpoints all the sets of images of the three time points obtained at Visit 2, one ceCT and one ^{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 for most of the reads. The readers will be specifically trained for this protocol.

All the images will be reviewed according to the workflow illustrated in Figure 2 and Figure 3 below.

Figure 2 Flow Chart of the Independent Review Methodology (68Ga-OPS202)

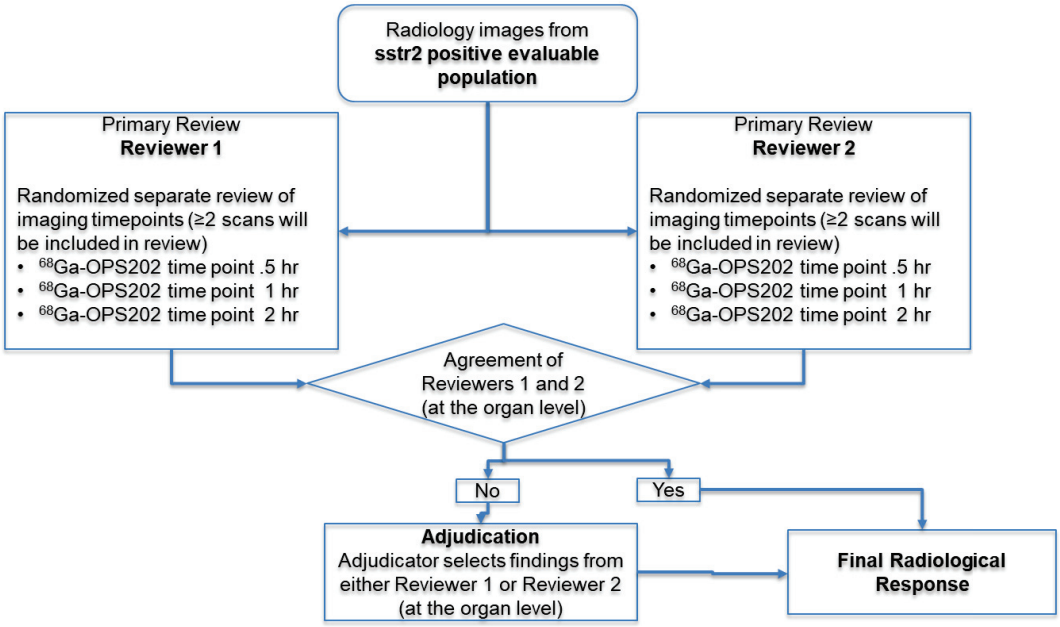
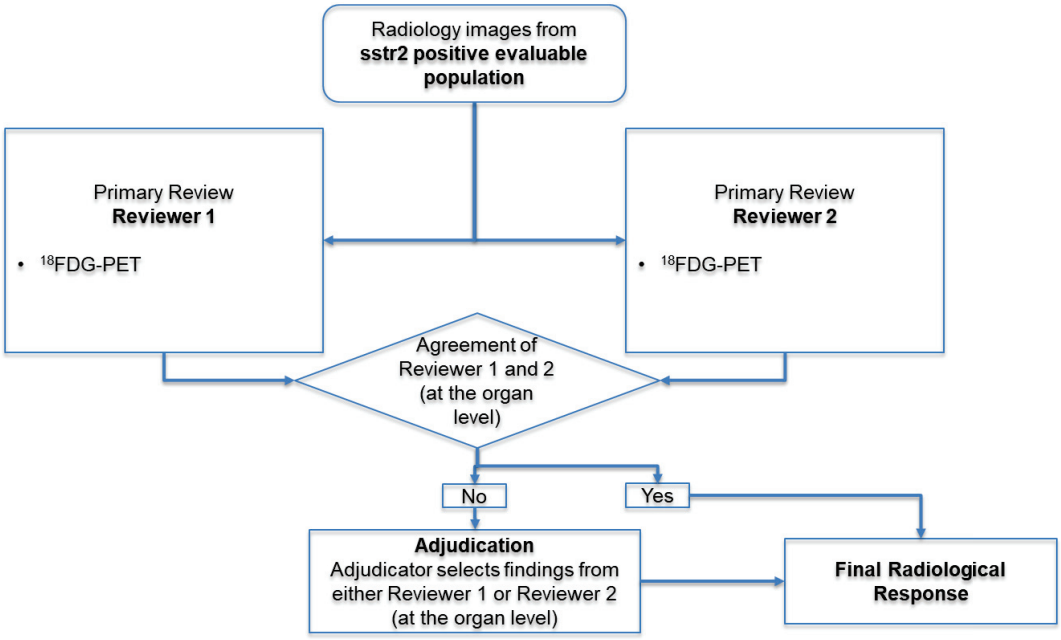


Figure 3 Flow Chart of the Independent Review Methodology (^{18}F-FDG-PET standard-of-truth)



Full details of the read design and conduct are provided in the Independent Review Charter (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. In case of discrepancy in lesion counts, images will go to the adjudicator (third reader) for a final read and adjudication.

For image quality, the readers will compare the three ^{68}Ga-OPS202 PET/CT scans contemporaneously for each subject and note which image(s), if any, provides superior images based on overall image quality and lesion count.

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

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

(1) Review of the 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 scans (with ceCT).

1.3.2.2 Safety assessments

- Adverse Events

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

AEs will be recorded and graded according to the current version of the National Cancer Institute Common Terminology Criteria for AEs (version 5.0, Dated 14 February 2018).

- Vital signs

Vital signs will be collected at Screening (Visit 1), IIP administration visit (Visit 2 Day 1 before IIP administration and at 0.5, 1, 2, 4 hours post-injection and on Day 2), and End of Study (Visit 3)/Early Withdrawal.

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

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

Any clinically significant abnormalities will be recorded as AEs.

- Physical Examination

Physical examination and body weight will be conducted at Screening (Visit 1), IIP administration visit (Visit 2 Day 1, Pre-Dose), and End of Study (Visit 3)/Early Withdrawal. 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.

- Electrocardiography

Electrocardiograms (ECGs) will be recorded at Screening Visit and EOS/EW (Visit 3).

Twelve-lead ECGs will be recorded at a paper speed of 25 mm/sec so that the different ECG intervals (RR interval, PR interval, QRS interval, QT and QTc) can be measured automatically as per study site usual practice.

The ECG will be recorded with the subject in supine position after five minutes of rest until four regular consecutive complexes are available. ECG interval estimates will be measured as per study site usual practice, in this study.

Any clinically significant abnormalities will be recorded as AEs.

- Clinical Laboratory Tests

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

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

The investigator will review the safety laboratory test results, document the review, and record any clinically relevant result occurring or observed during the study in the AE section of the eCRF.

Haematology – the following parameters will be assessed: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) absolute count (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) and platelet count.

Blood Biochemistry – the following parameters will be assessed: urea, creatinine, creatinine clearance, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, phosphate, alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine

aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, total protein, total cholesterol, triglycerides, fasting glucose

Urinalysis – the following parameters will be assessed: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocyte esterase, glucose and specific gravity by dipstick.

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

Pregnancy - A pregnancy test will be performed for all female subjects of childbearing potential at each visit: ß-HCG test at Screening and End of study and urinary hCG test at Visit 2 Day 1 before IIP administration).

1.3.2.3 Other assessments

The following assessments will be performed at Screening visit (Visit 1), that will take place within the 2-week period prior to the first ^{68}Ga-OPS202 administration:

- Demographic data (year of birth/age, sex and race/ethnicity will be collected according to individual country regulations/requirements).
- Subject disposition information
- Medical and surgical history, including ongoing conditions
- Prior and concomitant medications/therapies
- Prior and concomitant non-drug therapies
- Concomitant surgical procedures
- Collection of historical paraffin embedded breast tumour blocks or slides with anatomical location of the lesion (s) indicated.

1.3.2.4 Withdrawal/discontinuation

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

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.

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 and an explanation given of why the subject is withdrawing or being withdrawn from the study.

In case subject is lost to follow-up, date of termination will be specified, and the EW visit will be performed if possible.

1.3.3 Schedule of assessments

The schedule of procedures and assessments during the study is summarised in Table 1.

Table 1 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, physical examination, 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**: 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 others) 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}FDG-PET or ^{68}Ga-OPS202 post the 2-hour acquisition). Low-dose CT scans will be acquired for the other PET scans where 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 Imaging Review Charter (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.

1.3.4 Planned sample size

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 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 to ensure an adequate sample size in the sstr2 positive BC evaluable set.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

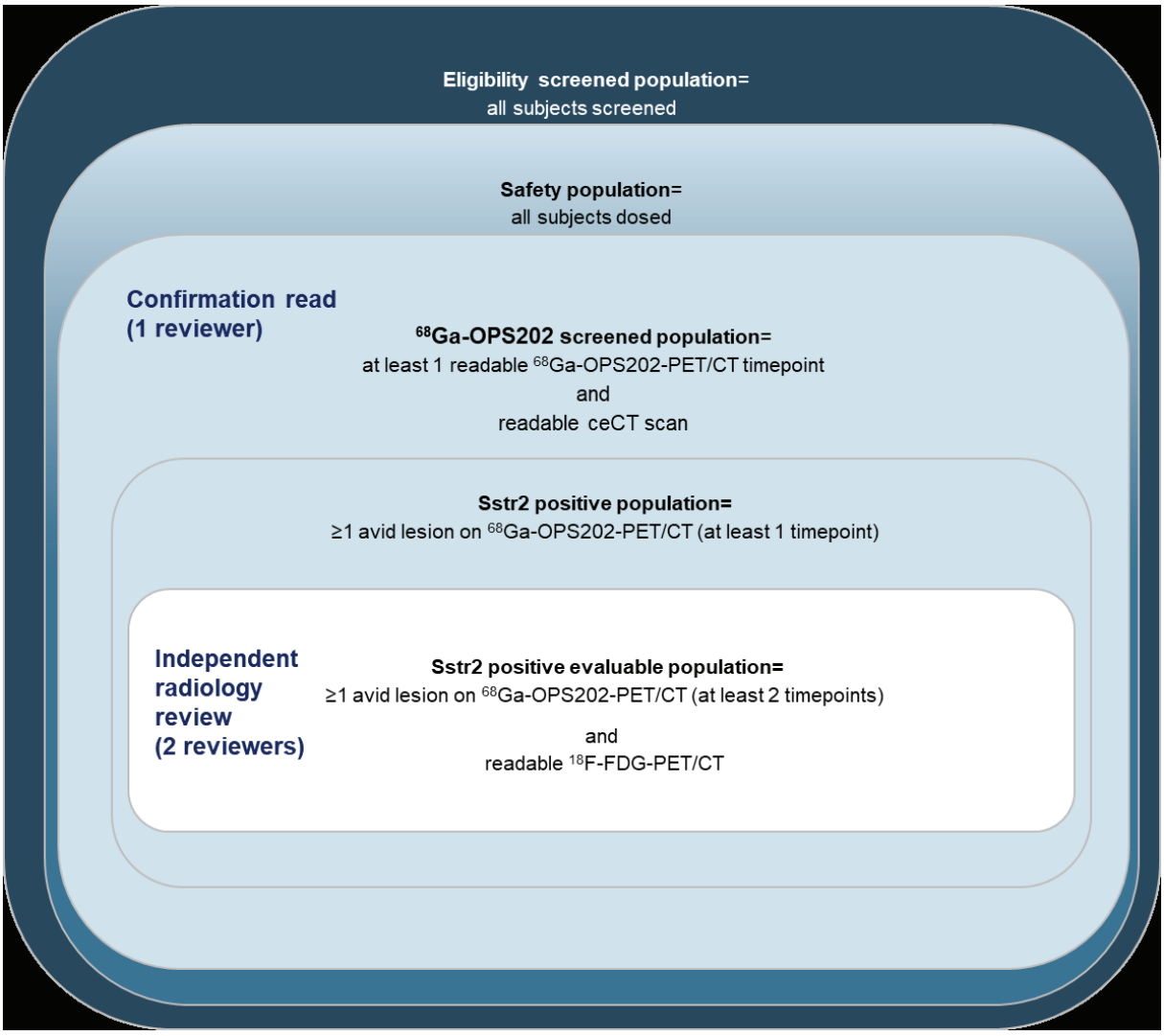
The following populations will be used during statistical analyses:

- **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. A ^{68}Ga-OPS202 timepoint is considered evaluable if it shows at least one avid lesion.

Study populations are summarized in the figure below.

Figure 4 Study populations



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

2.1 Efficacy populations

2.1.1 ^{68}Ga-OPS202 screened population

The ^{68}Ga-OPS202 screened population includes all subjects who received the dose of study IIP with one or more readable ^{68}Ga-OPS202 PET and a readable ceCT scan.

The assessment of ^{68}Ga-OPS202 PET scan and ceCT scan readability will be based on the imaging read named "Confirmation read", provided by ICL.

This population encompasses both subjects with sstr2 positive lesion(s) and those with sstr2 negative lesions (i.e. no avid lesion with ^{68}Ga-OPS202).

2.1.2 Sstr2 positive population

The sstr2 positive population includes 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.

The assessment of ^{68}Ga-OPS202 PET scan readability and the presence of avid lesions will be based on the imaging read named "Confirmation read", provided by ICL.

Subjects are also required to have a ^{18}F-FDG-PET/CT scan and a readable ceCT scan.

2.1.3 Sstr2 positive evaluable population

The sstr2 positive evaluable population includes all subjects from the ^{68}Ga-OPS202 sstr2 positive population with at least two evaluable timepoints. Subject are also required to have a ^{18}F-FDG-PET/CT scan and a readable ceCT scan.

Evaluable subjects are those with a ceCT scan, ^{18}F-FDG-PET scan and at least two ^{68}Ga-OPS202 PET scans that are readable (three images are to be acquired but two 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 on at least 2 timepoints by central readers.

The assessment of ^{68}Ga-OPS202 PET scan readability and the presence of avid lesions will be based on the blinded imaging read "^{68}Ga-OPS202 PET Independent Review" (two readers and potential adjudication), provided by ICL.

Listings of subjects regarding inclusion in each population and satisfying the population definition and associated data will be reviewed by the study team.

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

2.2 Safety population

The safety population includes all subjects who received the dose of study IIP.

A subject who received IIP but did not sign the informed consent will be included into the safety population.

2.3 Primary population

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, as a supportive post-hoc analysis, the sstr2 positive prevalence may also be evaluated on the agreed optimum timepoint population.

All secondary and exploratory efficacy endpoints will be evaluated on the sstr2 positive evaluable population.

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

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

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

Statistical analyses will be performed by Covance Clinical Development SARL.

3.1.1 Primary efficacy endpoints

The co-primary efficacy endpoints are:

(a) 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).

(b) 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. 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.

3.1.2 Secondary efficacy endpoints

Key Secondary Endpoint:

(c) 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.

(d) 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:

(e) 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).

(f) 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

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

Exploratory Endpoints:

(h) 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

(i) SNR calculated from lesion-free volume of interest (VOI) in the liver: SUV_{mean}/SUV_{SD} at the three PET acquisition timepoints

(j) Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG-PET

(k) Estimated correlation between ^{68}Ga-OPS202 PET uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

3.1.3 Safety endpoints

The safety and tolerability of ^{68}Ga-OPS202 will be assessed throughout the study by evaluating AEs, clinically significant abnormalities in laboratory tests (serum chemistry, haematology, and urinalysis), vital signs measurements (including blood pressure and heart rate), physical examination findings and body weight measurements, ECG findings, relevant medical history and concomitant medication/therapies usage.

The following safety endpoints will be evaluated:

- Percentage 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 adverse events (SAEs) and 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).
- Percentage 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.

3.1.4 Multiplicity

No multiple testing will be performed in this study.

3.1.5 Significance testing and estimation

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

3.2 Analysis methods

3.2.1 Efficacy

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

As specified in the description of each efficacy criterion thereafter, analysis will be based on PET/CT assessments for lesion count endpoints (absolute number of lesions, relative lesion count, image quality and diagnostic sensitivity) and on PET assessments alone for SUV related assessments.

The standard-of-truth (SOT) is the ^{18}F-FDG-PET/ceCT scan images acquired at any time during the study period (including the Screening period).

Due to decision of study premature termination, several analyses and/or outputs were removed.

3.2.1.1 Primary efficacy analysis

First component of the co-primary endpoint

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, i.e. the sstr2 positive prevalence in this study population. 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.

This will be a simple percentage calculation:

$$\text{Percentage of subjects with avid lesion identified as sstr2 positive lesion} = \frac{Number\ of\ subjects\ in\ sstr2\ positive\ population}{Number\ of\ subjects\ in\ 68Ga-OPS202\ \ screened\ population}$$

A listing with the subjects in sstr2 positive population and the subjects in the ^{68}Ga-OPS202 screened population will be provided in order to allow computing this percentage.

Second component of the co-primary endpoint

The second component of the co-primary endpoint is based on both image quality and lesion count using the sstr2 positive evaluable population.

The selection of the optimal PET acquisition time will be done by choosing the timepoint with superior images based on overall image quality and observed higher number of lesions detected.

The number of lesions detected by ^{68}Ga-OPS202 in the primary breast lesions will be reported at each of the three PET acquisition timepoints (0.5, 1 and 2 hours).

Individual values of number of lesions detected by ^{68}Ga-OPS202 in the primary breast lesions (result from both readers as well as final result) will be listed by subject and by PET acquisition timepoint.

Image quality

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.

This qualitative assessment will be performed using a quality score.

For each PET/CT assessment, each independent blinded reader will perform a direct comparison of the three ^{68}Ga-OPS202 scans acquired at different times (0.5, 1 and 2 hours) in the primary breast lesions. The readers will be allowed to select whether one, two or all three acquisitions are optimal, attributing a score for each assessment. The readers will be blinded to timepoint sequence.

The score for the assessment having superior images will be set to "1", and score for the assessments not selected will be set to "0". In case two assessments are considered optimal and of equal quality, both assessments will have a score of "1" and the third one will be set to "0". In case of equal quality between the three scans, the three assessments will have a score of "1".

Values will be available in the database provided by ICL.

In case a timepoint has been assessed as "non-readable" for the reader, the given timepoint will not be available for comparison, and therefore will have a missing quality score for that reader.

Individual values of quality score for primary breast lesions and reason for selecting scan will be listed per reader, by subject and by PET acquisition timepoint.

3.2.1.2 Secondary efficacy analysis

All secondary and exploratory analyses will be performed using the sstr2 positive evaluable population only.

Similar to the primary endpoint, the selection of the optimal PET imaging time of ^{68}Ga-OPS202 will be based on the provided outputs for all secondary and exploratory efficacy endpoints.

Key Secondary Endpoint:

a) Absolute number of lesions detected by ^{68}Ga-OPS202 in nodular and metastatic lesions

For each PET/CT assessment, the individual number of lesions detected by ^{68}Ga-OPS202 in nodular and metastatic lesions (result from both readers as well as final result) will be listed by subject and by PET acquisition timepoint. If there is a high number of lesions (≥35 lesions) in any one organ, identifying and counting of the lesions is not feasible as it cannot be accurately done. The absolute number of lesions will be presented as a category "≥35 lesions" if such case occurs.

Values will be available in the database provided by ICL.

A listing of all discrepancies between both readers in the nodular and metastatic lesions will also be presented by subject and PET acquisition timepoint.

Image quality

For each PET/CT assessment, each independent blinded reader will perform a direct comparison of the three ^{68}Ga-OPS202 scans acquired at different times (0.5, 1 and 2 hours) in nodular and metastatic lesions.

Individual values of quality score for nodular and metastatic lesions and reason for selecting scan will be listed per reader, by subject and by PET acquisition timepoint

b) Lesion SUV_{max} and tumour-to-background ratio

Lesion SUV_{max}

For each PET assessment, the SUV_{max} (unit-less measure) will be measured for each lesion, up to a maximum of the five most avid lesions per organ identified by one of the primary readers.

In order to obtain a unique measure per organ, the mean of the SUV_{max} will be computed within each of the six following organs:

- Primary breast lesion
- Liver
- Lymph nodes
- Bone
- Lungs
- Brain.

Values will be available in the database provided by ICL.

Tumour-to-background ratio

For each PET assessment, the tumour-to-background ratio will also be measured for each lesion, up to a maximum of the five most avid lesions per organ, as follow:

$$\text{Tumour to background ratio} = \frac{Lesion\ SUVmean}{SUVmean\ of\ the\ subject's\ reference\ tissue\ (tumour\ free\ liver\ *)}$$

*If insufficient tumour free liver is available for reference tissue, then aortic blood pool will be used as background.

The tumour-to-background ratio will be obtained using the mean of all lesions tumour-to-background ratios for each of the six following organs:

- Primary breast lesion
- Liver
- Lymph nodes
- Bone
- Lungs
- Brain.

Tumour-to-background ratio is a unit-less measure where a high tumour-to-background ratio indicates high effectiveness of ^{68}Ga-OPS202 as a diagnostic agent, in a similar manner to SUV_{max}.

Individual values of the lesion SUV_{max}, lesion SUV_{mean}, SUV_{mean} of the subject's reference tissue and tumour-to-background ratio will be listed by subject, by each of the six organs and by PET acquisition timepoint.

Other Secondary Endpoints:

c) Relative lesion count

The relative lesion count is the ratio of the number of lesions detected by ^{68}Ga-OPS202 at each of the three PET acquisition timepoints compared to the number of lesions assessed by standard-of-truth (^{18}F-FDG-PET scan).

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

$$Relative\ lesion\ count\ = \frac{Number\ of\ lesions\ detected\ by\ 68Ga-OPS202}{Number\ of\ lesions\ detected\ by\ 18\mathrm{F}-\mathrm{FDG}-\mathrm{PET}}$$

Relative lesion count will be computed over all lesions of all organs and for each of the following organs:

- Primary breast tumour (among all subjects with at least one lesion detected by ^{18}F-FDG-PET in primary breast tumour).
- Lymph nodes (among all subjects with at least one lesion detected by ^{18}F-FDG-PET in lymph nodes).
- Liver (among all assessed subjects with at least one lesion detected by ^{18}F-FDG-PET in liver).
- Axial/appendicular skeleton (bone) (among all assessed subjects with at least one lesion detected by ^{18}F-FDG-PET in bone).
- Lungs (among all assessed subjects with at least one lesion detected by ^{18}F-FDG-PET in lungs)
- Brain (among all assessed subjects with at least one lesion detected by ^{18}F-FDG-PET in brain).

For the per organ analysis, the relative lesion count will be:

- Equal to 0 if there is no lesion identified in the specific organ on ^{68}Ga-OPS202 scan.
- Missing if the numerator is missing (for example in case of non-readable ^{68}Ga-OPS202 PET scan at timepoint) with non-null denominator
- Not analyzed if there is no lesion identified in the specific organ on ^{18}F-FDG-PET scan.

If there are 35 lesions or more counted on both ^{68}Ga-OPS202 and ^{18}F-FDG-PET scans, then the relative lesion count will be set to 100%. If any of the two scans has a count of ≥35, the relative lesion count will be computed using a count of 35 lesions for the scan showing more than 35 lesions.

Individual values of the relative lesion count will be listed by subject, by organ and by PET acquisition timepoint.

d) Absolute number of lesions detected by ^{68}Ga-OPS202 in lymph nodes, liver, Axial/appendicular skeleton, lungs and brain

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

- Lymph nodes
- Liver
- Axial/appendicular skeleton (Bones)
- Lungs
- Brain

Values will be available in the database provided by ICL.

Individual values of the number of lesions detected by ^{68}Ga-OPS202 (results from both readers and final result) will be listed by subject, organ and PET acquisition timepoint.

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

This analysis will not be provided.

Exploratory efficacy endpoints:

f) 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

This analysis will not be provided.

g) SUV_{max} ratio for lesions

This analysis will not be provided.

h) SNR

For the primary breast lesions, the SNR will be computed as follows:

$$SNR = \frac{SUV_{mean}}{SUV_{SD}\ of\ the\ subject's\ reference\ tissue\ (tumour - free\ liver *)}$$

*If insufficient tumour free liver is available for reference tissue, then aortic blood pool will be used instead.

Values will be available in the database provided by ICL.

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

Individual values of SNR will be listed by subject and by PET acquisition timepoint.

i) Estimated correlation in terms of number of avid lesions between ^{68}Ga-OPS202 PET at the agreed "optimum timepoint" and ^{18}F-FDG-PET

This analysis will not be provided.

j) Estimated correlation between ^{68}Ga-OPS202 PET uptake and results of immunohistochemistry staining of sstr2 of the primary tumour.

This analysis will not be provided.

3.2.2 Safety

All safety data will be provided in both data listings and summary tables and using the Safety population.

3.2.2.1 Adverse events

All AEs will be recorded and graded by investigators using the NCI CTCAE classification (Version 5.0), will be coded using the MedDRA Version 20.1 or higher, and will be classified by MedDRA PT and SOC.

Listings will be presented and sorted by subject number, start date of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study.

Listings of SAEs, AEs leading to IIP withdrawal and AEs leading to death (fatal outcome) will also be presented. Also, a listing of grade ≥3 AEs will be provided.

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

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

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

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

(3) it was present prior to receiving the ^{68}Ga-OPS202 injection, the grade is the same but the causality changed to “related” during the study.

[redacted] CCI [redacted]

An overall summary table of all AEs will be presented.

In that table, in the cross classification of causality and intensity, any subject experiencing multiple AEs with different intensities for each causality category will be counted for each grade.

3.2.2.2 Laboratory data

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

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

Subject listings will be presented by subject number and visit.

- Haematology and Biochemistry

For haematology and biochemistry parameters, the baseline will be defined as the last measurement collected prior to IIP administration (Visit 2 Day 1).

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

Haematological and biochemistry toxicities will be recorded and graded according to the NCI-CTC criteria, Version 5.0. The NCI-CTC grade 3 and 4 haematology and biochemistry parameters by subject and by visit will be listed. Listings of the laboratory parameters in appendix 2 section 14.3.4 will include listings of NCI-CTC Grade 3 and 4 haematological toxicities, listings of NCI-CTC Grade 3 and 4 biochemical toxicities and listings of out of range biochemistry parameters that could not be graded using NCI-CTC grade (below Lower Limit of Normal range (LLN) – normal – above Upper Limit of Normal range (ULN).

- Urinalysis

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

3.2.2.3 Vital signs

Vital signs (body temperature, supine and standing blood pressure and heart rate, respiratory rate), body weight and BMI will be listed at each assessment by subject. Any unscheduled vital signs will be flagged [U] in the listing.

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

Summary statistics will be presented at each scheduled assessment for actual values and changes from baseline.

Following assessments will be summarised for body temperature, blood pressure, heart rate and respiratory rate: Baseline, 0.5h Post-dose, 1h Post-dose, 2h Post-dose, 4h Post-dose, Visit 2 Day 2, EOS/EW.

Weight and BMI will be analysed at Baseline, Visit 2 Day 2 and EOS/EW.

3.2.2.4 ECG

ECG results will be listed at each assessment (Screening, EOS/EW) by subject. Any unscheduled ECG will be flagged [U] in the listings.

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

For continuous ECG parameters (RR duration, PR duration, QRS duration, QT duration, QTc Bazett, QTc Fridericia, QTc manual) summary statistics will be presented at each scheduled assessment for actual values and changes from baseline.

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

3.2.2.5 Physical examination

Physical examination (normal, abnormal, specification for abnormal result) will be listed by subject number and visit. Any unscheduled physical examination will be flagged [U] in the listings.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

- Efficacy endpoints

No imputations will be made for missing data.

- Safety endpoints

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

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

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

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

3.2.3.2 Missing or incomplete dates

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

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

3.2.3.3 Outliers

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

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

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

3.2.4 Subject disposition

The numbers and percentages of subjects included in each of the Eligibility screened, Safety, ^{68}Ga-OPS202 screened, sstr2 positive and sstr2 positive evaluable population will be tabulated. The reasons for subject exclusions from each of the populations will also be tabulated.

A listing of dates and time of assessments (relative day) will be presented by subject.

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

The listing of subject disposition will include the subject exposure in the study. The definition of the study exposure is defined in the Appendix 1 Derived data.

3.2.5 Withdrawals

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

3.2.6 Demographic and baseline characteristics

In order to characterise the subjects, descriptive summary statistics (n, mean, SD, median, minimum, and maximum) or frequency counts of demographic and baseline data will be presented for the Safety population.

Summary statistics will be provided for demographic and baseline characteristics:

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

Summary statistics of the tumour characteristics will be provided:

- Tumour, node and metastasis (TNM) staging
- presence of metastases
- location of metastases
- Estrogen Receptor status
- Progesterone Receptor status
- IHC result
- ISH result

All demographic and baseline characteristics will be listed by subject.

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

3.2.7 Medical and surgical history

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

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

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary SOC and PT on the safety population.

3.2.8 Subject compliance

3.2.8.1 Subject exposure to IIP

Subject exposure to IIP will be described using the safety population presented in a summary table for the following data:

- Injection performed (yes/no)
- Injected peptide mass dose (µg)
- Injected radioactivity dose (MBq)

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

The exposure information will be presented on separate listings as follows:

First subject listing will present the IIP preparation by subject, with following information:

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

Second subject listing will be presented for the IIP administration, by subject, with following information:

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

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

3.2.8.2 Protocol deviations

All the protocol deviations identified will be listed by subject.

3.2.9 Prior and concomitant therapies

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

All recorded data will be included in data listings.

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

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

3.2.9.1 Prior and concomitant medications

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

Medications that started and stopped before study IIP administration are considered as prior medications. Medications that started before study IIP administration but are continuing will be considered as both prior and concomitant medications.

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

A frequency table of the number and percentage of subjects will be provided for prior medications and concomitant medications by therapeutic class and PT on the safety population.

3.2.9.2 Prior and concomitant non-drug therapies

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

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

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

A frequency table of the number and percentage of subjects will be provided by SOC and PT on the safety population.

3.2.9.3 Concomitant medications for breast cancer

Concomitant medications for breast cancer will be coded using WHO-DD, version June 2016 or higher. Medications which started and stopped before study IIP administration are considered as prior medications for breast cancer.

Medications which started before study IIP administration but are continuing will be considered as both prior and concomitant medications for breast cancer.

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

A frequency table of the number and percentage of subjects will be provided by therapeutic class and PT on the safety population.

3.2.9.4 Concomitant surgical procedures

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

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

A frequency table of the number and percentage of subjects will be provided for concomitant surgical procedures by SOC and PT on the safety population.

3.2.10 Derived data

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

3.2.11 Rules and data formats

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

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

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

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

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

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

3.2.12 Pooling of Centres

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

3.2.13 Interim analysis

No interim analysis will be performed. One final analysis will be performed at the end of the study, after database lock.

3.2.14 Covariates and analysis of subgroups

It is not planned to perform such analysis.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using Windows 7 or newer.

4.2 Software

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

4.3 Validation programs

SAS® programs are developed to produce clinical study output such as analysis data sets, summary tables, data listings or statistical analyses. SOP CCI "Programming specifications for analysis data sets" provides an overview of the development of such SAS® programs.

SOP CCI "Verification of statistical programs and output" describes the quality control procedures that must be performed for all SAS® programs and outputs. Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS® programs produce the proper clinical study output by checking for their logic, efficiency and commenting, and by inspection of the produced outputs.

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

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

4.4 Restitution of the programs

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

5 CHANGES FROM PROTOCOL

- Section 3.2: The SAP Version 2.0 was revised to remove some of the planned analyses stated in the study protocol. The decision to remove some of the planned analyses (in particular, efficacy endpoints are not summarized in tables) was based upon the limited data. A decision had been made to prematurely terminate this study and at that time, there was limited data collected on the study.

6 REFERENCES

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

7 DATA PRESENTATION

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