Journal of Nuclear Medicine, published on October 12, 2017 as doi:10.2967/jnumed.117.199737

Safety, Biodistribution, and Radiation Dosimetry of ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11) in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase I Imaging Study

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Number of words: 5091

Short running title: ^{68}Ga-OPS202 PET/CT imaging phase I study

ABSTRACT

Preclinical and preliminary clinical evidence indicates that radiolabeled somatostatin receptor (sst) antagonists perform better than agonists in terms of detecting neuroendocrine tumors (NETs). This prospective phase I/II study is the first to evaluate an sst antagonist, ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11; NODAGA=1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid and JR11=Cpa-c(DCys-Aph(Hor)-DAph(Cbm)-Lys-Thr-Cys)-DTyr-NH_2)) for PET imaging. Here, we report results of the phase I component of the study.

Methods: Patients received two single intravenous injections of 150 MBq ^{68}Ga-OPS202 three to 4 weeks apart (15 µg peptide at visit 1 and 50 µg at visit 2). At visit 1, a dynamic PET/CT scan was performed over the kidney during the first 30 min post-injection and static whole-body scans at 0.5, 1, 2, and 4 h p.i; at visit 2, a static whole-body scan was performed at 1 h. Blood samples and urine were collected at regular intervals to determine ^{68}Ga-OPS202 pharmacokinetics. Safety, biodistribution, radiation dosimetry, and the most appropriate imaging time-point for ^{68}Ga-OPS202 were assessed.

Results: Twelve patients with well-differentiated gastroenteropancreatic (GEP)-NETs took part in the study. ^{68}Ga-OPS202 rapidly cleared from the blood; the mean residence time in the blood was 2.4 ± 1.1 min/L. The organs with the highest mean dose coefficients were the urinary bladder wall, kidneys, and spleen. The calculated effective dose was 2.4E-02 ± 0.2E-02 mSv/MBq, corresponding to 3.6 mSv for a reference activity of 150 MBq. Based on total numbers of detected malignant lesions, the optimal time window for the scan was between 1 and 2 h. For malignant liver lesions, the time point at which most patients had the highest mean tumor contrast was 1 h. ^{68}Ga-OPS202 was well tolerated; adverse events were grade 1 or 2 and there were no signals of concern for laboratory blood or urinalysis tests.

Conclusion: ^{68}Ga-OPS202 shows favorable biodistribution and imaging properties with optimal tumor contrast between 1 and 2 h post-injection. Dosimetry analysis revealed that ^{68}Ga-OPS202 delivers a

similar dose to organs as other ^{68}Ga-labeled somatostatin analogs. Further evaluation of ^{68}Ga-OPS202 for PET/CT imaging of NETs is therefore warranted.

Keywords: neuroendocrine tumors; somatostatin receptor antagonist; dosimetry; ^{68}Ga-OPS202; ^{68}Ga-NODAGA-JR11

INTRODUCTION

Neuroendocrine tumors (NETs) can occur in almost any organ, but are most commonly observed in the pancreas and gastrointestinal tract (*1*). Diagnosis is delayed by 3-10 years on average (*2*) and an estimated 40-95% of gastroenteropancreatic (GEP)-NETs are metastatic by the time of diagnosis (*3*). Excluding benign insulinomas, more than 90% of all GEP-NETs express a high density of somatostatin receptor subtype-2 (sst_2) (*4*). As such, ssts have been exploited as molecular targets for imaging and treating GEP-NETs. Indeed, the use of radiolabeled somatostatin analogs has become an integral part of the management of patients with these tumors, facilitating localization of the primary tumor, staging, and restaging (*3*). They can also be used as 'theranostic' agents, to determine the level of sst expression, select and treat appropriate patients with unlabeled or radiolabeled somatostatin analogs (*5*).

Sst imaging was initially developed using scintigraphy or single-photon emission computed tomography (SPECT) with ^{111}In- or ^{99m}Tc-labeled sst agonists (*6*). Until recently, ^{111}In-pentetreotide (Octreoscan) was the most widely used radiolabeled sst analog. Currently, positron emission tomography/computed tomography (PET/CT) imaging using ^{68}Ga-DOTA-Tyr^3-Octreotide (^{68}Ga-DOTATOC = ^{68}Ga-edotreotide) is associated with a significantly higher detection rate compared with conventional sst scintigraphy (*6*). This reflects higher scanner sensitivity and greater spatial resolution for PET/CT versus SPECT imaging (*6*), as well as the higher affinity of ^{68}Ga-DOTATOC for sst_2 (*7*). Alternatively, ^{68}Ga-DOTA-Tyr^3-Octreotate (^{68}Ga-DOTATATE) has comparable diagnostic accuracy to ^{68}Ga-DOTATOC (*8*). In a direct comparison of ^{68}Ga-DOTATOC PET/CT and triple-phase CT, specificity was 97.4%, but sensitivity was only 72.8% in a lesion-based analysis (*9*). High diagnostic sensitivity is mandatory for planning surgery and other treatments; thus, there is a clinical need for further improvement of sst imaging in patients with GEP-NETs.

The use of radiolabeled antagonists rather than agonists has the potential to improve sst PET/CT imaging, as antagonists may recognize a higher number of somatostatin receptor binding sites (*10*).

Furthermore, in the first clinical study of an sst antagonist (^{111}In-DOTA-BASS) in cancer patients, tumor uptake and lesion detection rates were higher than with ^{111}In-pentetreotide (*11*). However, ^{111}In-DOTA-BASS is a SPECT tracer with its above-described limitations. For this reason, a small library of sst_2 antagonists was developed for PET/CT imaging; of these, NODAGA-JR11 (OPS202) was selected as it demonstrated the highest affinity for sst_2 when labeled with ^{68}Ga (*12,13*). Results of an *in vivo* biodistribution study comparing ^{68}Ga-DOTATATE (agonist) with ^{68}Ga-NODAGA-JR11 (^{68}Ga-OPS202) and ^{68}Ga-DOTA-JR11 have shown that ^{68}Ga-OPS202 is the radiopharmaceutical of choice for clinical translation, on the basis of its very high tumor uptake and excellent biodistribution profile (*13*). Here, we present the results of the phase I component of a phase I/II study, which evaluated the safety, biodistribution, radiation dosimetry, and optimal imaging time point of ^{68}Ga-OPS202 in patients with GEP-NETs.

MATERIALS AND METHODS

Study design

This was an open-label micro-dosing phase I/II study performed at a single specialist center in Basel, Switzerland (NCT02162446; EudraCT No. 2014-001881-88). The Institutional Review Board approved this study, and all subjects signed a written informed consent in accordance with the Declaration of Helsinki. There were four study visits: a screening visit; visit 1 (within 28 days of the screening visit), during which the first dose ^{68}Ga-OPS202 (15 µg, 9.03 nmol OPS202) was administered; visit 2 (3-4 weeks after visit 1), during which the second dose of ^{68}Ga-OPS202 (50 µg, 30.1 nmol OPS202) was administered; and the end-of-study visit 3 (7-15 days after visit 2) for patient follow-up.

Patients

The main inclusion criteria were: age ≥18 years; histologically confirmed diagnosis of well-differentiated GEP-NET; Karnofsky status ≥60; prior diagnostic CT/magnetic resonance imaging scan of the tumor region and positive sst scan (^{68}Ga-DOTATOC PET/CT) in previous 6 months; ≤30 lesions per organ; and ≥10% of liver in tumor-free state. Patients were excluded if they had: previous or current allergic or autoimmune disease; active infection at screening or serious infection in the previous 6 months; treatment with NET-specific agents between the last sst scan and the start of the study, except somatostatin analogs, provided that there was a sufficient wash-out period (28 days for long-acting and 2 days for short-acting analogs).

Synthesis and radiolabeling

OPS202 was synthesized according to good manufacturing practice by Bachem AG, Switzerland. ^{68}Ga-OPS202 was prepared on an automated synthesis unit (PharmTracer, Eckert & Ziegler) by loading the eluate of a ^{68}Ge/^{68}Ga-generator (GalliaPharm™, Ecker & Ziegler) onto the cation exchange column. ^{68}Ga was eluted with a mixture of 5 M NaCl/HCl (*14*) directly into the reaction vial containing an adjusted

amount of OPS202, depending on the intended amount to be administered. OPS202 was radiolabeled at 75°C within 400 s, followed by C18 solid-phase extraction, with radiochemical purity ≥95%.

Imaging

Patients received a first intravenous injection of 15 µg and 150 MBq ± 25% (mean ± SD) ^{68}Ga-OPS202 (visit 1) over ≤1 minute; the actual administered amount consisted of 14 ± 4 µg peptide, range [11 – 19 µg]. After injection, the cannula was flushed with normal saline and removed from the patient in order to measure the residual activity (including the syringe); the effective administered activity was 161 ± 21 MBq, range [125 – 189 MBq]. The second administration of ^{68}Ga-OPS202 (visit 2) consisted of 50 ± 15 µg [37 – 63 µg] / 150 MBq ± 25%; effective administered activity 172 ± 14 MBq [141 – 192 MBq]. Other medication was permitted, except the administration of diuretics on the day of ^{68}Ga-OPS202.

Three-dimensional (3D) PET scans were acquired at visits 1 and 2 using the same PET/CT scanner (Discovery^{TM} STE, GE Healthcare). The effective administered activity (defined as the activity in the syringe before minus residual activity in the empty syringe after injection) was used for PET image reconstruction. Calibration and quality assurance were performed with ^{68}Ga in analogy to the EARL accreditation procedure with ^{18}F-FDG (http://earl.eanm.org/cms/website.php): the scanner was cross-calibrated to a well-counter calibrated for ^{68}Ga using a homogenously filled phantom; image quality and resolution was assessed using a NEMA-Phantom with spheres of various size.

A low-dose, non-enhanced CT scan was acquired using the following parameters: 120 keV, current modulation (smart 30-300 mA), 0.8s/rotation and pitch 1.75. All PET scans were acquired 4 min/bed position with 5-slice overlap. Attenuation corrected PET images were reconstructed using the standard GE proprietary 3D iterative reconstruction (3 mm FWHM; 21 subsets; 2 iterations, 128×128 matrix for a 70-cm-diameter FOV).

At visit 1, a dynamic scan was conducted over the kidney region during the first 30 min; static scans were conducted from head to sub-inguinal region at 0.5, 1, 2, and 4 h post-injection. At visit 2, a static

scan was performed from head to sub-inguinal region 1 h post-injection. Two independent, qualified readers (one on-site and one central), blinded with regards to patient and peptide dose reviewed the scans. Assessments were done in each body region in the following order: liver, lymph nodes, bone, and other organs. Volumes of interest were used to measure maximal standardized uptake values (SUV_{max}) for each lesion and reference tissues located in the direct vicinity of the lesion. Biodistribution of 15 and 50 µg ^{68}Ga-OPS202 were compared 1 h post-injection using SUV_{max} measured in the following normal organs: pituitary, parotid, thyroid, lung, mediastinum, liver, spleen, pancreas, stomach, jejuno-ileum, adrenals and muscle.

In order to determine the optimal imaging time window, scans obtained at 0.5, 1, 2, and 4 h during visit 1, were evaluated according to the absolute numbers of detected lesions, SUV_{max} for tumors and for reference tissues, and mean image contrast values (tumor-to-background ratios: SUV_{max} [tumor]/SUV_{max} [reference tissue]). The evaluation was done by the central reader.

Radiation dosimetry

For visit 1 (15 µg peptide dose), organs with visible uptake were identified on PET and delineated manually on PET/CT fusion images, using a prototype version of MintLesion™ (Mint Medical GmbH, Dossenheim, Germany). Volume of interest (VOI) were drawn over the whole body and the following organs: pituitary, parotids, thyroid, lungs, mediastinum, liver, pancreas, spleen, adrenals, kidneys, gastro-intestinal tract, urinary bladder, and vertebral bodies L2-L4, in order to determine the relative activity in each organ at each time point. Patient-specific individual organ sizes taken from the CT Scans were used to determine the uptake of the whole organ. No recovery correction was applied.

Time-activity curves (unit: % of injected activity within each (VOI) as function of time) were derived, taking renal excretion activity into account. By using NUKFIT software (*15*) these curves were fitted by mono- or bi-exponential curves and integrated to yield the corresponding time-integrated activity coefficients (“residence times”). Absorbed radiation dose for each organ was calculated using the

dosimetry software, OLINDA v.1.1 (*16*), according to the following parameters and assumptions: ^{68}Ga; adult male model; no bladder voiding model; equal distribution of residence times for the stomach, small intestine, upper large intestine, and lower large intestine. For bone marrow dosimetry, blood-based values for the red bone marrow residence times were calculated according to the method described by Herrmann et al. (*17*). In addition, an image-based red bone marrow residence time was calculated by integrating the LV2-LV4 time-activity curve assuming that 6.7% of the total bone marrow is contained in LV2-LV4 (*17*).

Organ dose coefficients (mGy/MBq) were calculated, taking individual organ contributions into account as calculated by OLINDA. The effective dose per actual administered activity (mSv/MBq) was also calculated, applying the ICRP 60 tissue weighing factors (*18*).

Blood samples were taken to determine time-activity curves pre-dose and at 2, 5, 10, 20, and 30 min, as well as at 1, 2, and 4 h post-injection. Urine was also collected to determine the renal excretion of ^{68}Ga. Voids were collected from 0 to 2 h and from 2 to 4 h post-injection. Total radioactivity concentration in whole blood and urine was determined using a gamma-counter (Cobra II, Packard Instrument Company).

Safety assessments

The primary objective of the study was to evaluate the safety and tolerability of ^{68}Ga-OPS202. These were assessed at visits 1, 2, and 3 (end of study) by recording vital signs (up to 4 h post-injection), physical examination, clinical laboratory tests (hematology, biochemistry, urinalysis) at each visit and performing a 12-lead electrocardiogram (2.5 h post-injection and at visit 3). Adverse events (AEs) were recorded and graded according to CTCAE 4.03.

Statistical analysis

All variables were analyzed descriptively. Wilcoxon signed-rank test, with a p-value <0.05 denoting statistical significance, was used to compare 15 and 50 µg doses (matched pairs).

RESULTS

Patients

Twelve patients were screened and took part in the study. All patients completed the study and were included in the dosimetry, pharmacokinetic, and safety evaluations. Baseline demography and disease characteristics are summarized in Table 1 and in Table 1 of the accompanying phase II part of the study.

Biodistribution and pharmacokinetics

The mean (SD) residence time in the blood was 2.4 (1.1) min/L. Fig. 1 shows the whole-body biodistribution of ^{68}Ga-OPS202 one hour after its injection in a patient with an ileal NET, who was in complete remission at the time of imaging. Fig. 2 shows the whole-body biodistribution at 0.5, 1, 2, and 4 h in another patient with ileal NET.

Statistical analysis revealed subtle but significantly lower mean background activity (SUV_{max}) at visit 2 (50 µg dose) vs. visit 1 (15 µg dose) in the liver, stomach, and jejuno-ileum (Table 2).

Optimal imaging time window

The overall number of malignant lesions at visit 1 was highest with good reproducibility in the 1 h and 2 h scan and lowest in the 4 h scan: 152 (0.5 h), 162 (1 h), 164 (2 h), and 121 (4 h), see Fig. 2. Similarly, the total number of liver metastases was highest in the 1h and 2 h scan: 125 (0.5 h), 135 (1 h), 137 (2 h), and 96 (4 h). The total number of lymph node lesions remained almost constant: 19 in the first three scans and 18 in the 4 h scan.

For liver metastases, the time point at which most patients had the highest and most reproducible median image contrast (median tumor-to-background ratio with the normal liver as reference tissue) was 1 h, see Fig. 2 and Supplemental Fig. 1. This was also the case for lymph node metastases (normal lymph node as reference).

Radiation dosimetry

Mean time-integrated activity coefficients and mean dose coefficients are shown in Tables 3 and 4, respectively. For the calculation of the bone marrow contribution to the absorbed doses the image-based residence times were used as a conservative estimate as they were generally higher than the corresponding blood-based values. The organs with the largest time-integrated activity coefficients were the urinary bladder, liver, kidneys, and lung. The organs with the highest mean dose coefficients were the urinary bladder wall, kidneys and the spleen. The calculated mean (SD) effective dose was 2.4E-02 (0.2E-02) mSv/MBq, which represents 3.6 mSv for an injection of 150 MBq ^{68}Ga-OPS202.

Safety

Overall, 11 Adverse events (AEs) were reported in 6 patients. Of these, AEs were grade 1 in 4 patients and grade 2 in 2 patients. The relationship to ^{68}Ga-OPS202 was deemed 'not related' in one patient, 'unlikely' in three patients, and 'possible' in two patients (Table 5). There was no grade 3 (severe), 4 (serious), or 5 (fatal) AEs.

The most frequently reported AEs were urinary tract infection and fatigue. For other AEs see Table 5. Three AEs in two patients were assessed as possibly related to treatment: eosinophilia, rash, and diarrhea. All were grade 1 in intensity and none required drug treatment.

Overall, eight patients had clinically significant abnormal laboratory results at least once during the study period. In most cases, these abnormalities were also either documented at screening or as medical history findings. Furthermore, the number of patients with abnormal hematology, biochemistry, or urinalysis results did not increase from baseline over the course of the study, and no aggravating effect of ^{68}Ga-OPS202 on already abnormal renal or hepatic parameters was observed. ^{68}Ga-OPS202 did not affect body weight, vital signs, the electrocardiogram, or the physical examinations.

DISCUSSION

This is the first clinical study to evaluate a ^{68}Ga-labeled sst antagonist for PET/CT imaging. The results show that in patients with GEP-NETs, the organs with the highest dose coefficients were the bladder wall, kidneys, and spleen. The results obtained for the bladder wall and kidneys are consistent with this class of compounds and the renal elimination of ^{68}Ga-OPS202.

Data from dosimetry studies with ^{68}Ga-labeled sst agonists (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC = ^{68}Ga-DOTA,1-Nal^{3}-Octreotide) and results from the current study showed comparable calculated mean (SD) effective doses: 2.4E-02 (0.2E-02) mSv/MBq for ^{68}Ga-OPS202, 2.6E-02 (0.3E-02) mSv/MBq and 2.1E-02 (0.3E-02) mSv/MBq for ^{68}Ga-DOTATATE (*19,20*), 2.1E-02 (0.3E-02) mSv/MBq for ^{68}Ga-DOTATOC (*20*), and 2.5E-02 (0.5E-02) mSv/MBq for ^{68}Ga-DOTANOC (*21*). However, there are differences in the biodistribution among these tracers resulting in different organ doses. The most pronounced differences are found for the liver, lung and spleen. The mean (SD) liver dose was: 2.2E-02 (0.9E-02) mGy/MBq for ^{68}Ga-OPS202; 4.5E-02 (1.5E-02) and 5.0E-02 (1.5E-02) mGy/MBq for ^{68}Ga-DOTATATE (*19,20*); 4.1E-02 (1.4E-02) mGy/MBq for ^{68}Ga-DOTATOC (*20*); and 3.4E-02 (1.0E-02) mGy/MBq for ^{68}Ga-DOTANOC (*21*). The low liver uptake and dose of ^{68}Ga-OPS202 are likely to be clinically relevant as, compared to ^{68}Ga-DOTATOC, ^{68}Ga-OPS202 exhibits substantially higher tumor-to-background ratios and sensitivity for detecting liver metastases (see for reference the results of the Phase II study, summarized in the accompanying paper). The mean (SD) lung dose was 2.1E-02 (0.7E-02) mGy/MBq for ^{68}Ga-OPS202 and between 0.6E-03 and 1.2E-02 mGy/MBq for ^{68}Ga-labeled sst agonists.

Slight differences were observed in the biodistribution of the two doses of ^{68}Ga-OPS202 (15 and 50 µg, respectively) 1 h post-injection. The liver, stomach, intestine and pancreas showed either a trend or significantly lower background uptake with the higher peptide amount. The reason for this finding in the

liver, reputed sst_2-negative, is unknown and there are notable exceptions among sst_2 expressing organs e.g. the pituitary and the adrenals possibly impacted by their small size and the high partial volume effects affecting the accuracy of the uptake measure. In any case, this is an important feature, as a lower background activity in organs that are potentially sites of primary or metastatic disease may improve tumor detection. However, this did not translate in significantly different tumor-to-background ratios and number of detected metastases (when on-site reader only was taking into account) between the 2 peptide doses. This is probably because of the small difference in the amount of peptide and the limited sample size. Nevertheless, this finding suggests that receptor saturation of physiologically expressed sst_2 occurs at an early stage of dose escalation in organs expressing sst_2 and is consistent with the results of our pre-clinical evaluation using larger peptide amounts (*22*).

The current study also evaluated the optimal imaging window for ^{68}Ga-OPS202. Based on image contrast data, number of detected lesions and reproducibility, the optimal image window is between 1 and 2 h. PET/CT scans for other ^{68}Ga-labeled sst ligands are also acquired at approximately 1 h (*23*).

The administration of ^{68}Ga-OPS202 was well tolerated. Most AEs were grade 1 and there was no grade 3, 4, or 5 AEs. Furthermore, there were no signals of concern for any of the laboratory blood tests or urinalysis results. When reported, most of the abnormal laboratory findings were related to underlying diseases (e.g. chronic kidney disease, diabetes mellitus) or to urinary tract infections. There were three AEs assessed as possibly related to treatment: grade 1 eosinophilia in one patient, and rash and diarrhea (both grade 1) in another. Mild hypereosinophilia is a non-specific finding that may accompany number of conditions (e.g. infections, asthma and allergies, vasculitis, and non-hematological malignancies), but also can occur as a drug reaction. Other ^{68}Ga-labeled somatostatin analogs are also well tolerated. No clinical adverse reactions were reported with ^{68}Ga-DOTATOC (*21*) and with ^{68}Ga-DOTATATE; and there were no changes in physiologic responses, blood counts, electrolytes, liver function tests, or renal function (*19*).

One of the limitations of the study is the small patient number, which is, however, typical for this stage of early drug development. The number of patients evaluated in dosimetry studies of the ^{68}Ga-labeled sst agonists was also small (n = 6-10) (*19-21*). Other limitations relate to the study design. First, the crossover design was not 2-way, i.e. none of the patients received the higher peptide dose first. Second, extended follow-up was not conducted to evaluate the longer-term safety profile of ^{68}Ga-OPS202. However, this is not expected to be an issue given the short half-life of the radionuclide, the low radiation burden, and the low amount of peptide, which is likely to be too low to exert pharmacological activity. The main strength of the study is the use of PET/CT-based 3D dosimetry, which allows higher spatial resolution and more precise delineation of organ-bound activity compared with 2D dosimetry.

CONCLUSION

This phase I study shows that ^{68}Ga-OPS202 is rapidly cleared from the blood, resulting in low background activity, especially in the liver and gastro-intestinal tract. Accordingly, administration of ^{68}Ga-OPS202 delivers an acceptable radiation dose to organs. The effective dose is comparable to ^{68}Ga-labeled sst agonists that are already established in the clinic. Furthermore, there were no safety signals of concern. Further evaluation of ^{68}Ga-OPS202 for PET/CT imaging of NETs and other sst_2 expressing tumors is therefore warranted.

DISCLOSURE

Jean E.F. Rivier, Jean Claude Reubi, and Helmut R. Maecke, who are co-inventors of somatostatin-based antagonistic radiopeptides, assigned all their patent rights to their respective academic institution. Hakim Bouterfa is a founder of OctreoPharm Sciences GmbH and a former employee of Ipsen; he now

acts as a consultant for Ipsen. Jens Kaufmann is an employee of Ipsen. This study was sponsored by Ipsen.

ACKNOWLEDGMENTS

We thank all the patients who participated in the trial, the OctreoPharm/Ipsen team, the personnel of the Division of Radiopharmaceutical Chemistry and Nuclear Medicine (University Hospital Basel), John Uiters and Nils Schreiter from Medwave Medical imaging. We thank Judit Erchegyi, Charleen Miller and Josef Gulyas for their early contribution to the synthesis/characterization of the peptide reagents. We also would like to thank Nicky French (Watermeadow Medical®) for medical writing support (funded by Ipsen). Jean E. F. Rivier is “The Dr. Frederik Paulsen Chair in Neurosciences Professor.”

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TABLE 1

Baseline demography and disease characteristics

Parameter	Total (n=12)
Age, mean (SD) in years	54.8 (14.7)
Gender, n (%)	
Male	7 (58.3)
Female	5 (41.7)
Time since GEP–NET diagnosis, mean (SD) in years	4.8 (8.51)
Grade, n (%)	
G1	8 (67)
G2	4 (33)
GEP–NET hormonal status, n (%)	
Functioning	5 (41.7)
Non-functioning	7 (58.3)
Somatostatin Receptor Analog, n (%)	
Yes	6 (50)
Schemes	
Octreotide or Lanreotide Depot form /4 weeks	6 (50)
Octreotide daily s.c.	0 (0)

SD, standard deviation; GEP-NET, gastroenteropancreatic neuroendocrine tumors; s.c., subcutaneous injection

TABLE 2

Mean background activity in organs at 1h post-injection of 15 µg (visit 1) and 50 µg (visit 2) ^{68}Ga-OPS202

Organ	Mean (SD) SUV_{max}		p-value
	Visit 1 15 µg peptide	Visit 2 50 µg peptide	
Liver	3.2 (0.8)	2.9 (0.7)	<0.05
Stomach	4.2 (2.3)	3.0 (1.2)	<0.05
Jejuno-ileum	3.5 (1.3)	2.9 (0.7)	<0.05
Pancreas	3.2 (2.0)	2.6 (1.4)	0.052
Parotids	3.7 (1.9)	3.4 (1.7)	0.06
Right adrenal	7.4 (3.7)	6.3 (2.3)	0.09
Left adrenal	8.3 (3.9)	7.1 (3.5)	0.08
Pituitary	5.8 (1.8)	5.7 (2.0)	0.23
Thyroid	2.3 (1.2)	2.3 (0.7)	0.93
Lung	1.7 (0.6)	1.6 (0.6)	0.29
Mediastinum	1.7 (0.5)	1.5 (0.3)	0.18
Spleen	11.7 (4.2)	10.1 (2.3)	0.14

SD, standard deviation; SUV_{max}, maximal standardized uptake values

TABLE 3

Residence times in organs following single injection of ^{68}Ga-OPS202

Organ	Mean (SD) residence time Minutes
Whole body	80.22 (4.38)
Urinary bladder wall	5.16 (1.80)
Liver	4.32 (1.20)
Kidneys	3.42 (0.84)
Lung	2.64 (0.60)
Blood	2.40 (1.08)
Spleen	1.62 (1.02)
Red bone marrow*	1.32 (0.60)
Stomach	1.08 (0.18)
Lower large intestine	1.08 (0.18)
Upper large intestine	1.08 (0.18)
Small intestine	1.08 (0.18)
Heart	0.72 (0.24)
Pancreas	0.12 (0.06)
Vertebral bodies (L2–4)	0.12 (0.06)
Adrenal glands	0.06 (0.000)
Gallbladder	0.06 (0.000)

SD, standard deviation; *Blood-based residence time calculation

TABLE 4

Dose coefficients in organs following single injection of ^{68}Ga-OPS202

Organ	Mean (SD) dose coefficient mGy/MBq
Urinary bladder wall	1.01E-01 (4.28E-02)
Kidneys	8.43E-02 (3.13E-02)
Spleen	6.02E-02 (4.73E-02)
Lower large intestine wall	3.54E-02 (1.03E-02)
Adrenal glands	2.99E-02 (1.16E-02)
Upper large intestine wall	2.60E-02 (6.98E-03)
Stomach wall	2.30E-02 (7.53E-03)
Liver	2.18E-02 (8.66E-03)
Lung	2.12E-02 (7.01E-03)
Small intestine	1.89E-02 (4.50E-03)
Pancreas	1.55E-02 (5.09E-03)
Heart wall	1.47E-02 (3.83E-03)
Osteogenic cells	1.39E-02 (3.55E-03)
Gallbladder wall	1.22E-02 (3.10E-03)
Uterus	1.19E-02 (1.72E-03)
Red marrow	1.13E-02 (3.08E-03)
Ovaries	1.10E-02 (1.68E-03)
Testes	8.52E-03 (1.70E-03)
Muscle	8.50E-03 (1.68E-03)
Thymus	8.41E-03 (1.73E-03)
Thyroid	8.04E-03 (1.73E-03)
Breasts	7.45E-03 (1.70E-03)
Brain	7.32E-03 (1.72E-03)
Skin	7.13E-03 (1.69E-03)

SD, standard deviation

TABLE 5

Summary of Adverse Events following single dose of ^{68}Ga-OPS202

Patient No	Adverse Event (AE)	Intensity (CTCAE 4.03)	Relation of AE
1	Urinary tract infection	Grade 2	Unlikely
3	Abdominal pain	Grade 1	Not related
	Urinary tract infection	Grade 1	Not related
	Abnormal liver function test	Grade 1	Unlikely
5	Eosinophilia	Grade 1	Possible
	Fatigue	Grade 1	Unlikely
7	Fatigue	Grade 2	Unlikely
8	Nasopharyngitis	Grade 1	Not related
11	Rash	Grade 1	Possible
	Diarrhea	Grade 1	Possible
	Headache	Grade 1	Unlikely

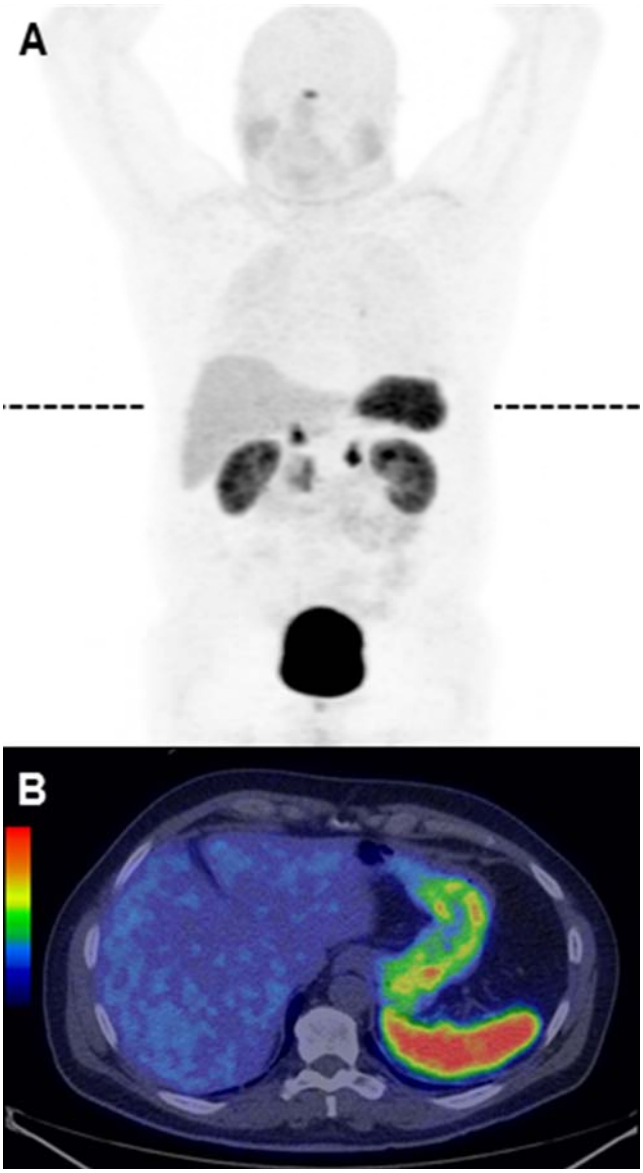


FIGURE 1. Biodistribution of 175 MBq ^{68}Ga-OPS202 (15 µg) 1 h post-injection in patient 11 with NET of the ileum. Currently the patient is in complete remission. (A) Shows the whole-body PET scan and dotted lines show the level of the transaxial PET/CT slice (B). There is low background activity in the salivary glands, liver and intestine.

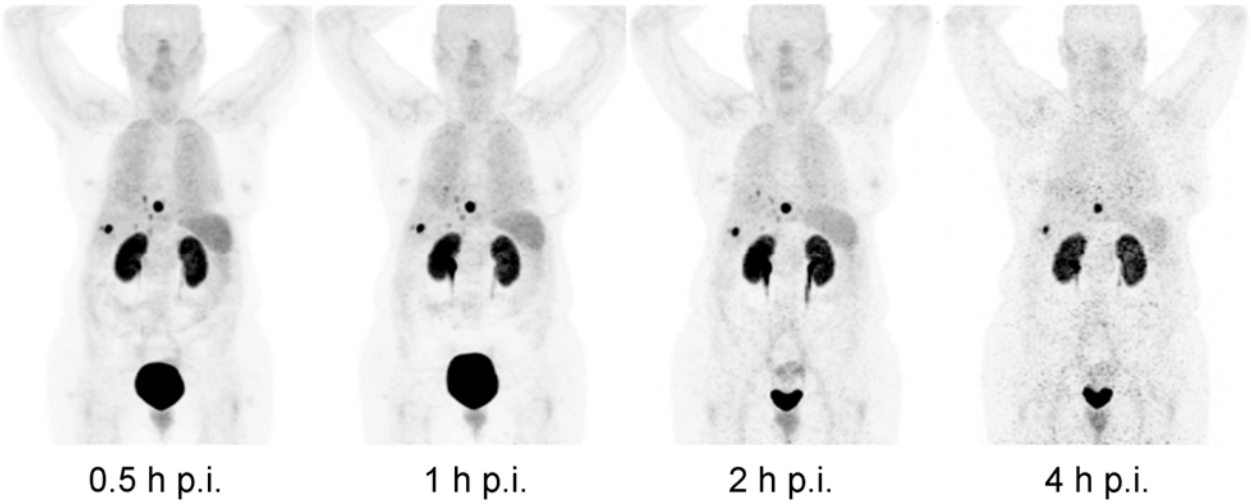
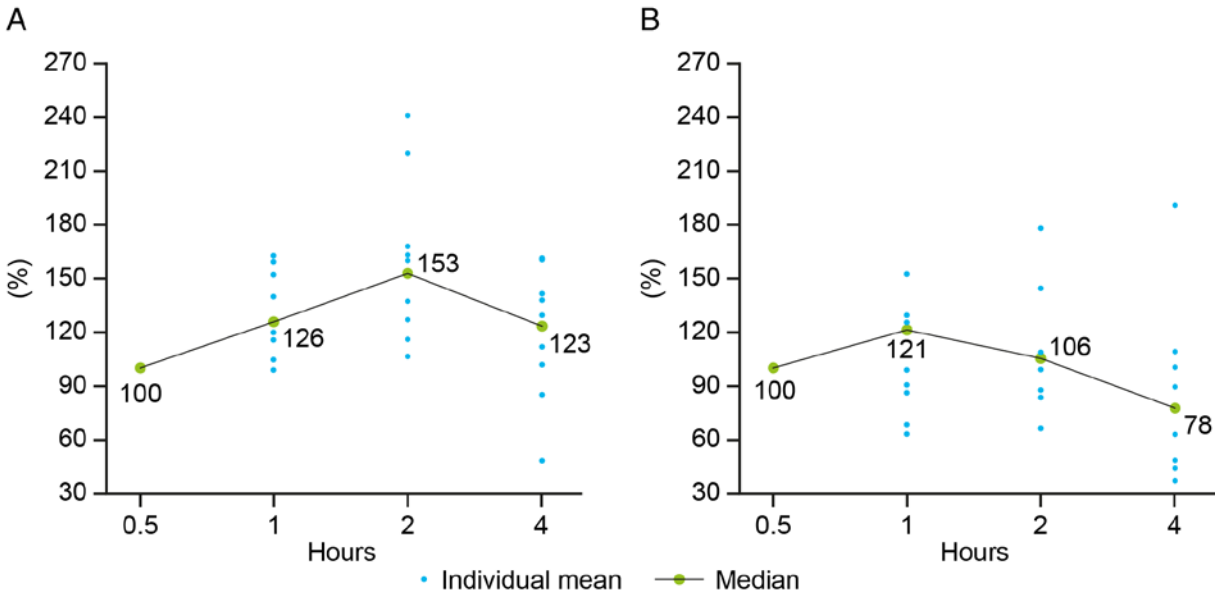


FIGURE 2. Biodistribution of 188 MBq ^{68}Ga-OPS202 (15 µg) at 0.5, 1, 2, and 4 h post-injection in patient 2 with an ileal NET. PET Maximum Intensity Projections with a constant linear gray scale show multiple liver metastases and subdiaphragmal peritoneal deposits. Tumor and renal uptake persist over time while organs such as spleen, lungs and liver, along with the urinary excretion are progressively washed out. The highest tumor contrast was found at 1 h post-injection, while 4h images suffer from poor count statistics. There is remarkably low accumulation of ^{68}Ga-OPS202 in sst_2 positive organs such as pituitary, spleen, adrenals and uncinate process of the pancreas.

Supplementary Information



SUPPLEMENTAL FIGURE 1. Tumor-to-background ratios normalized to the first timepoint (0.5h) for matched lesions identified at all timepoints (liver metastases). (A) Data from on-site reader. (B) Data from central reader. Tumor-to-background ratios: SUV_{max} [tumor]/SUV_{max} [reference tissue]