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Comparison of ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11) and ^{68}Ga-DOTATOC (^{68}Ga-Edotreotide) PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors: Evaluation of Sensitivity in a Prospective Phase II Imaging Study

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ABSTRACT

Radiolabeled somatostatin receptor (sst) agonists are integral to the diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), but detection rates, especially of liver metastases, remain limited even with PET/CT. ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11), a novel radiolabeled sst antagonist with a high affinity for sst_2, has the potential to perform better than sst agonists. Here we present the results of the Phase II component of a Phase I/II study, which evaluated the sensitivity of ^{68}Ga-OPS202 PET/CT compared with the reference compound, ^{68}Ga-DOTATOC (sst agonist).

Methods: Patients received a single intravenous administration of ^{68}Ga-DOTATOC (15 µg peptide) and ^{68}Ga-OPS202 (15 µg peptide at visit 1; 50 µg peptide at visit 2) with an activity of 150 MBq. Whole-body PET/CT acquisitions were performed 1 h post injection on the same calibrated PET/CT scanner. Diagnostic efficacy measures were compared against contrast medium-enhanced CT or MRI as gold standard. Two independent blinded experts read the scans and both outcomes were combined for analysis.

Results: Twelve consecutive patients with G1 or G2 GEP-NETs took part in this prospective study. Image contrast for matched malignant liver lesions was significantly higher for ^{68}Ga-OPS202 scans than for the ^{68}Ga-DOTATOC scan: median of the mean [interquartile] tumor-to-normal-liver SUV_{max} ratios for 15 µg and 50 µg ^{68}Ga-OPS202 (5.3 [2.9 – 5.7] and 4.3 [3.4 – 6.3], respectively) were significantly higher than for ^{68}Ga-DOTATOC (1.9 [1.4 – 2.9]; p=0.004 and p=0.008, respectively). The higher tumor-to-background ratio of ^{68}Ga-OPS202 resulted not only in a higher detection rate of liver metastases, but also in a significantly higher lesion-based overall sensitivity with the antagonist than with ^{68}Ga-DOTATOC PET/CT: 94% and 88% for 50 µg and 15 µg ^{68}Ga-OPS202 and 59% for 15 µg ^{68}Ga-DOTATOC, respectively (p<0.001). Positive predictive values (PPVs) for ^{68}Ga-OPS202 PET/CT and ^{68}Ga-DOTATOC PET/CT were similar (approximately 98%). There were no significant differences between the two ^{68}Ga-OPS202 peptide doses in terms of image contrast, sensitivity or PPVs, indicating a high reproducibility.

Conclusion: Preliminary efficacy data from this Phase II study indicate that ^{68}Ga-OPS202 has high sensitivity for the detection of GEP-NETs. Further studies in larger patient populations are warranted.

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

INTRODUCTION

Gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are the most frequent neuroendocrine neoplasms (NENs), accounting for approximately two-thirds of all NENs.

Molecular imaging of NETs facilitates not only earlier diagnosis, but often detection of the primary tumor site, which is unknown in approximately 20-30% of cases (*1*). It also aids selection of the most appropriate therapy, thus improving outcomes (*2*). For many years, imaging with somatostatin receptor (sst) scintigraphy and single-photon emission computed tomography (SPECT) have been central to the diagnostic work-up of patients with NETs (*3*). More recently, it has been shown that positron emission tomography/computed tomography (PET/CT) scanning with ^{68}Ga-labeled sst agonists is superior to scanning with ^{111}In- or ^{99m}Tc-labeleled sst analogs (*4*). This reflects the greater sensitivity and spatial resolution of PET/CT, as well as the higher affinity of ^{68}Ga-radiopharmaceuticals for sst subtype 2 (sst_2) (*5,6*). ^{68}Ga production is also cost-effective, as portable ^{68}Ge/^{68}Ga-generators are available, allowing radioisotope access without the need for an onsite cyclotron. Another advantage of PET/CT versus SPECT/CT is that it permits better quantification of absolute tumor uptake. Although ^{68}Ga-DOTATOC PET/CT has very high sensitivity versus conventional ^{111}In-pentetreotide (Octreoscan®), the detection rate of liver metastases and its overall sensitivity was lower than that of hepatic phase MRI in a lesion-based analysis (*7,8*). This lack of sensitivity is an issue when it comes to planning surgery and liver directed therapies. Thus, there remains a clinical need for further improvement of sst imaging in patients with NETs.

The introduction of ^{68}Ga-labeled sst antagonists has the potential to improve NET imaging, as sst antagonists bind more receptor binding sites than sst agonists (*9*). The feasibility of using a radiolabeled antagonist (^{111}In-DOTA-BASS) was demonstrated in patients with NETs (n=4) or metastatic thyroid cancer (n=1) (*10*). Indeed, compared with traditional ^{111}In-pentetreotide (Octreoscan®) scintigraphy,

^{111}In-DOTA-BASS imaging was more sensitive. However, ^{111}In DOTA-BASS has low affinity for sst_2, which is the most common sst subtype expressed by NETs (*11*). Therefore a series of radiolabeled sst antagonists with higher affinity for sst_2 was developed (*12*). Among them ^{68}Ga-OPS202 was selected as the radioligand of choice based on its potential for imaging NETs (*13*). The corresponding therapeutic radiotracer ^{177}Lu-OPS201 (^{177}Lu-DOTA-JR11) for a theranostic approach was associated with tumor doses that were 1.7–10.6-fold higher than those observed with the sst agonist, ^{177}Lu-DOTATATE in four patients with metastasized NETs (*14*).

The first study of ^{68}Ga-OPS202 in human was designed to evaluate its safety, biodistribution, and dosimetry (Phase I) and its preliminary diagnostic efficacy (Phase II) in patients with GEP-NETs. The results of the Phase I study, which are summarized in the accompanying paper, show that there were no safety concerns with ^{68}Ga-OPS202 and that the mean effective dose of ^{68}Ga-OPS202 was 3.6 ± 0.3 mSv/150 MBq. For the Phase II component, the hypothesis was that ^{68}Ga-OPS202 would be a more sensitive agent than ^{68}Ga-DOTATOC PET/CT for diagnosis of GEP-NETs, with a high positive predictive value (PPV). The results presented in this publication follow the STARD 2015 statement, see checklist in the supplemental material.

MATERIALS AND METHODS

The methodology of the study (NCT02162446; EudraCT No. 2014-001881-88) is described in detail in the accompanying phase I part of the study. The institutional review board approved this study and all subjects signed a written informed consent in accordance with the Declaration of Helsinki.

Study design and patient population

This was a prospective, open-label, micro-dosing phase I/II study. Consecutive patients with a histologically confirmed well-differentiated low (G1) or intermediate grade (G2) GEP-NET were included if they had a positive ^{68}Ga-DOTATOC scan in the previous 6 months. Patients were excluded if they had received NET-specific treatments between the ^{68}Ga-DOTATOC scan and the start of the study, except somatostatin analogs, provided that there was a sufficient wash-out period (2 days for subcutaneous octreotide and 28 days for octreotide LAR or lanreotide Autogel [Depot in USA]). Potentially eligible patients were identified based on the date of their last or planned ^{68}Ga-DOTATOC scan in our clinic (between January and November 2014) and consultation of their medical records.

Synthesis and radiolabeling

Following elution from the ^{68}Ge/^{68}Ga-generator, ^{68}Ga was extracted using cation exchange. OPS202 and DOTATOC were labeled at 75°C and 95°C, respectively within 400 sec, followed by C18 solid-phase extraction to achieve purity ≥95%. For more detail, see the methods section of the phase I part of the study, in the accompanying paper.

Imaging

Patients received a first intravenous administration of ^{68}Ga-OPS202 (visit 1) with 14 ± 4 µg (mean ± SD) OPS202, range [11 - 19 µg], and an activity of 150 MBq ± 25% ^{68}Ga; actual administered activity 161 ± 21 MBq (mean ± SD), range [125 – 189 MBq] over ≤1 minute. Three to 4 weeks later the patients

received a second administration of ^{68}Ga-OPS202 (visit 2): 50 ± 15 µg, range [37 – 63 µg]) / 150 MBq ± 25%; actual administered activity 172 ± 14 MBq [141 – 192 MBq]. ^{68}Ga-DOTATOC: was administered in the same way as visit 1 (15 ± 5 µg / 161 ± 11 MBq). Use of diuretics was not permitted on scan days.

Three-dimensional (3D) whole body (head to sub-inguinal region) PET scans were performed 1 h after injection of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC using the same PET/CT scanner (Discovery™ STE, GE Healthcare). Calibration and quality assurance were performed according to the EARL procedure. For more detail, see the methods section of the phase I part of the study, in the accompanying paper.

Contrast enhanced CT and MRI scan

Referring centers performed follow-up imaging either with contrast-enhanced triple phase multidetector CT or MRI using 1.5 or 3T systems with a dedicated body array coil for signal reception 3 - 9 months after the End of Core Trial. Minimal pulse sequence requirements for MRI comprised axial and coronal T2-weighted sequences and axial multiphasic T1-weighted gradient echo sequences before and after administration of a gadolinium-based contrast agent. Additional (optional) pulse sequences included diffusion-weighted imaging and delayed T1-weighted imaging in in case of the use of hepatobiliary contrast agents.

Image analysis

Both ^{68}Ga-OPS202 scans and the reference ^{68}Ga-DOTATOC scan were reviewed by two independent, qualified readers, one on-site (board-certified Nuclear Medicine Physician from University Hospital Basel) and one central reader, who is a board-certified Radiologist and Nuclear Medicine Physician. Both readers were blinded with regards to patient, radiopharmaceutical, and peptide dose. Sequential locked-read methodology was used for image interpretation, i.e. once scans had been reviewed and

completed, readers were not permitted to re-read them and modify their opinion. As an image reading tool MintLesion™ (Mint Medical GmbH, Dossenheim, Germany) was used by both readers.

Diagnostic efficacy measure was: absolute numbers of malignant lesions detected. Additional measures were part of an explorative extension and are not part of the original design: standardized uptake values (SUV_{max}) for tumors and reference tissues; and mean tumor-to-background contrast values (SUV_{max} [tumor]/SUV_{max} [organs]). Reference tissues were muscle, liver, and lymph nodes, as well as normal tissue located in the immediate vicinity of a suspected focus of uptake. The results for each of these measures were compared between the 1 h ^{68}Ga-OPS202 PET/CT scans (15 and 50 µg) vs. the 1 h ^{68}Ga-DOTATOC scan, which is an accepted state-of-the-art imaging modality for GEP-NETs worldwide. Analysis of the SUV_{max} and tumor-to-background ratios was conducted for matched lesions only (i.e. only lesions that were present on the ^{68}Ga-DOTATOC scan as well as on both ^{68}Ga-OPS202 scans). In addition, the 1 h ^{68}Ga-OPS202 scan at visit 1 (15 µg peptide) was compared with the 1 h ^{68}Ga-OPS202 scan at visit 2 (50 µg peptide), to evaluate the reproducibility of tumor uptake, image contrast (tumor-to-background uptake ratios), and sensitivity measurements.

Sensitivity and positive predictive value

For sensitivity and PPV analyses, 1 h scans (for both ^{68}Ga-OPS202 doses and for ^{68}Ga-DOTATOC) were compared with clinical and imaging follow-up up to 9 months after the end of the core trial by the central reader who is a Nuclear Medicine Physician and Radiologist. As standard of reference, multiple phase abdominal CT, contrast enhanced MRI of the liver and/or in one case biopsy were used for comparison. Sensitivity and PPV analyses were part of an explorative extension and are not part of the original study design.

Statistical analysis

It was planned to recruit 12 patients for this Phase I/II study. This number was considered appropriate for an exploratory study and sufficient to address the study aim.

The non-parametric Wilcoxon signed-rank test was used to compare the number of identified lesions, the SUV_{max} for lesions and reference tissues, and the tumor-to-background uptake values for the visit 1 and visit 2 ^{68}Ga-OPS202 1 h scans (15 and 50 µg) vs. the reference ^{68}Ga-DOTATOC scan. Matched data from the on-site reader were used for the quantitative analysis of SUV values (median of the mean).

For the lesion-based sensitivity and PPV analyses, outcomes from on-site and central readers were considered to fit a mixed-effects logistic regression model. For exposure variables, it was assumed that scan method was a fixed-effect and patient and reader, random effects. Three tests of superiority were performed, ^{68}Ga-DOTATOC PET/CT versus 15 and 50 µg ^{68}Ga-OPS202 and 15 versus 50 µg ^{68}Ga-OPS202. To assess whether results are robust, only outcomes of the on-site reader were considered and compared with results from both readers. Statistical testing was exploratory. Level of significance was set at 5% and tests were two-sided. Indeterminate and missing values were not replaced.

RESULTS

Patients

The study profile is given in Fig. 1. Out of the 12 patients screened 12 were enrolled and all 12 completed the study and were included in the phase II diagnostic efficacy evaluations. Baseline demography and clinical characteristics are summarized for each patient in Table 1 and for the overall study population in the accompanying paper. The median [interquartile range] time between the ^{68}Ga-DOTATOC scan and the first ^{68}Ga-OPS202 scan (visit 1, 15 µg) was 34 [27.5 - 135]) days. One patient had the ^{68}Ga-DOTATOC PET/CT scan 16 days after visit 1. Both the ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT scans revealed disease in 11 of 12 patients. Follow-up imaging confirmed that patient 11 was in complete remission. Patients did not receive any treatments between ^{68}Ga-DOTATOC PET/CT and ^{68}Ga-OPS202 PET/CT scans. There were 11 AEs reported in six patients after injection of ^{68}Ga-OPS202, but none were severe, serious, or fatal (for more information, see phase I part of the study).

^{68}Ga-OPS202 vs. ^{68}Ga-DOTATOC PET/CT scan

The total numbers of malignant lesions and liver lesions were significantly greater with the ^{68}Ga-OPS202 scans than with ^{68}Ga-DOTATOC PET/CT (Table 2). There was no significant difference between the scans for the number of malignant lymph nodes. Due to the small number of patients with lesions in other organs/tissues statistical comparisons were not feasible.

Image contrast (tumor-to background ratio) for matched malignant liver lesions was significantly higher for ^{68}Ga-OPS202 than for ^{68}Ga-DOTATOC scan (Fig. 2 and Table 3). This was mainly due to the significantly lower SUV_{max} of liver background (Fig. 3 and 4) in the ^{68}Ga-OPS202 scans (Table 3). For matched malignant lymph nodes, there were no significant differences in the median of the mean

tumor-to-background ratios for ^{68}Ga-OPS202 scans vs. the ^{68}Ga-DOTATOC scan, regardless of the reference tissue.

Sensitivity and positive predictive value

Outcome analyses of both readers revealed a significantly higher lesion-based sensitivity for both 15 and 50 µg ^{68}Ga-OPS202 PET/CT compared to ^{68}Ga-DOTATOC PET/CT (both $p<0.001$) (Table 4, Fig. 3 and 4). There was also a significant difference in sensitivity between 15 and 50 µg ^{68}Ga-OPS202 ($p<0.05$), but was not confirmed in the assessment of robustness ($p=0.76$), i.e. if analysis was done using on-site readings only. The PPVs for all three tested PET tracers were around 98%.

DISCUSSION

This is the first study to evaluate the diagnostic efficacy of a radiolabeled sst antagonist, ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11), for PET/CT imaging of GEP-NETs. Of key importance are the results compared with the reference sst agonist PET/CT scan, which was conducted using ^{68}Ga-DOTATOC. Multiple phase CT of the abdomen and contrast enhanced MRI of the liver were performed during follow-up. These are the most accurate methods for establishing the presence or absence of neuroendocrine liver metastases (*3*) and were chosen as standard of reference. These show that ^{68}Ga-OPS202 is more sensitive than ^{68}Ga-DOTATOC PET/CT (88-94% vs. 59%), mainly because of a higher detection rate of liver metastases, the predominant site of metastases in patients with GEP-NETs (*15*). This reflects the significantly lower uptake of ^{68}Ga-OPS202 into the normal liver tissue and therefore the enhanced image contrast over ^{68}Ga-DOTATOC. This is likely to impact on patient management as the presence and extent of liver metastases is the most important prognostic factor (*16*). Unlike liver metastases, ^{68}Ga-OPS202 imaging did not detect more malignant lymph node lesions. This may reflect the much smaller sample size for these lesions vs. liver lesions.

Uptake of ^{68}Ga-OPS202 into normal pancreas and gastro-intestinal tract was lower than with ^{68}Ga-DOTATOC, leading to increased tumor-to-background uptake ratios and therefore, suggesting that it may be more useful for detecting primary GEP-NETs. This, in turn, could have a positive impact on clinical management as currently, the site of the primary tumor is unknown in approximately 20% of cases (*1*). Further studies are required to evaluate this aspect of diagnostic efficacy for ^{68}Ga-OPS202 PET/CT; it was not possible in the current study because of the small patient population and therefore the low overall numbers of primary lesions.

JR11 when coupled with NODAGA is an antagonist with high affinity for sst_2 (*12*) and shows more sst binding sites than the agonists ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC (own unpublished data). Based on

the results of preclinical imaging studies using radiolabeled JR11 conjugates in comparison with ^{68}Ga-DOTATATE (*12*), the tumor uptake of ^{68}Ga-OPS202 was expected to be higher than with ^{68}Ga-DOTATOC. In our clinical study this was not the case. This unexpected finding might be explained by the short half-life of Gallium-68 (68 min) that does not allow scans to be acquired at later time points. Posttreatment scans with its therapeutic sister compound, ^{177}Lu-OPS201 (^{177}Lu-DOTA-JR11) showed the highest tumor uptake between 3 and 24 hours after injection of the radiotracer (*14*), see supplemental Fig. 1. The sst agonist ^{177}Lu-DOTATATE showed a different behavior with the highest tumor uptake at around 1 hour after injection of the radiotracer, see supplemental Fig. 1.

As well as ^{68}Ga-DOTATOC, other ^{68}Ga-labeled sst agonists for PET/CT imaging include ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC. Like ^{68}Ga-OPS202, ^{68}Ga-DOTATATE is an sst_2-specific tracer, while ^{68}Ga-DOTANOC targets sst_2, sst_3, and sst_5 subtypes (*17*). The most commonly expressed ssts on GEP-NETs are sst_2 and to a lesser extent sst_1 and sst_5 (*11*). The clinical use of ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC was compared in a crossover study in 18 patients with GEP-NETs (*17*). Uptake values for liver tumors (median SUV_{max}) for ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC were similar to those obtained for ^{68}Ga-OPS202 in the current study, while uptake values for normal liver were lower with ^{68}Ga-OPS202, resulting in much better tumor-to-liver uptake ratios; median of the mean tumor-to-background uptake ratios were 2.0 for ~30 µg ^{68}Ga-DOTATATE and 2.7 for ~30 µg ^{68}Ga-DOTANOC (*17*), compared with 5.3 for 15 µg ^{68}Ga-OPS202, 4.3 for 50 µg ^{68}Ga-OPS202, and 1.9 for ~15 µg ^{68}Ga-DOTATOC in the present study. Although indirect comparisons with studies using other ^{68}Ga-labeled somatostatin analogs should be interpreted with caution, higher hepatic background levels have been consistently reported in the literature for ^{68}Ga-labeled sst agonists, compared to ^{68}Ga-OPS202. In the study of Wild et al. (*17*), median SUVmax [interquartile range] in the normal liver with ~30 µg ^{68}Ga-DOTATATE and ~30 µg ^{68}Ga-DOTANOC was 7.5 [5.6 – 9.8] and 5.1 [4.1 – 5.8] while in the current study, corresponding values of 15 µg ^{68}Ga-DOTATOC,

15 μg ^{68}Ga-OPS202 and 50 μg ^{68}Ga-OPS202 were 6.5 [4.8 – 8.9], 3.4 [2.7 – 3.6] and 2.7 [2.5 – 3.1]. This is consistent with the study of Poeppel et al. comparing ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC PET/CT with a mean (range) peptide amount of 6 μg (2 – 13) failing to show any major difference between the two tracers (*18*). These findings add weight to our conclusion that ^{68}Ga-OPS202 has improved imaging contrast for liver metastases compared with sst agonists.

The results obtained for the two doses of the peptide component of ^{68}Ga-OPS202 were generally consistent. There were no significant differences in the numbers of malignant liver or lymph node lesions detected per patient, the tumor and reference tissue uptake values, or the tumor contrast values indicating a high reproducibility of ^{68}Ga-OPS202 PET/CT imaging. This might be relevant for treatment response evaluation and follow-up imaging. There were no safety issues identified with either dose (see phase I paper), although the three adverse events (all Grade 1) assessed as possibly related to the study drug were reported in two patients examined with the higher dose (50 μg). Due to the radioactive decay of ^{68}Ge/^{68}Ga-generators, it is not practical to keep the radioactivity-to-mass dose ratio constant (specific activity), but the results of the current study indicate that OPS202 amounts between 15 and 50 μg are efficient, well tolerated and show a high reproducibility.

One of the limitations of the study was the small patient population. Whilst this is typical of early phase II studies, it does affect the power of statistical comparisons. Nevertheless, it does allow general trends to be evaluated and provides important information for future studies. It is notable that three of the 12 patients included in the study had more than 30 lesions. To avoid any possible bias the number of lesions per patients was taken into account for statistical analysis.

CONCLUSION

The preliminary efficacy data from the current study indicate that ^{68}Ga-OPS202 has high sensitivity, and reproducibility for the detection of GEP-NETs. These results, together with the safety profile from the Phase I evaluation suggest that ^{68}Ga-OPS202 might be a valuable new radiopharmaceutical for staging, localization, treatment response evaluation and follow-up imaging of NETs. Further studies in larger patient populations are warranted.

DISCLOSURE

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 in part by Ipsen.

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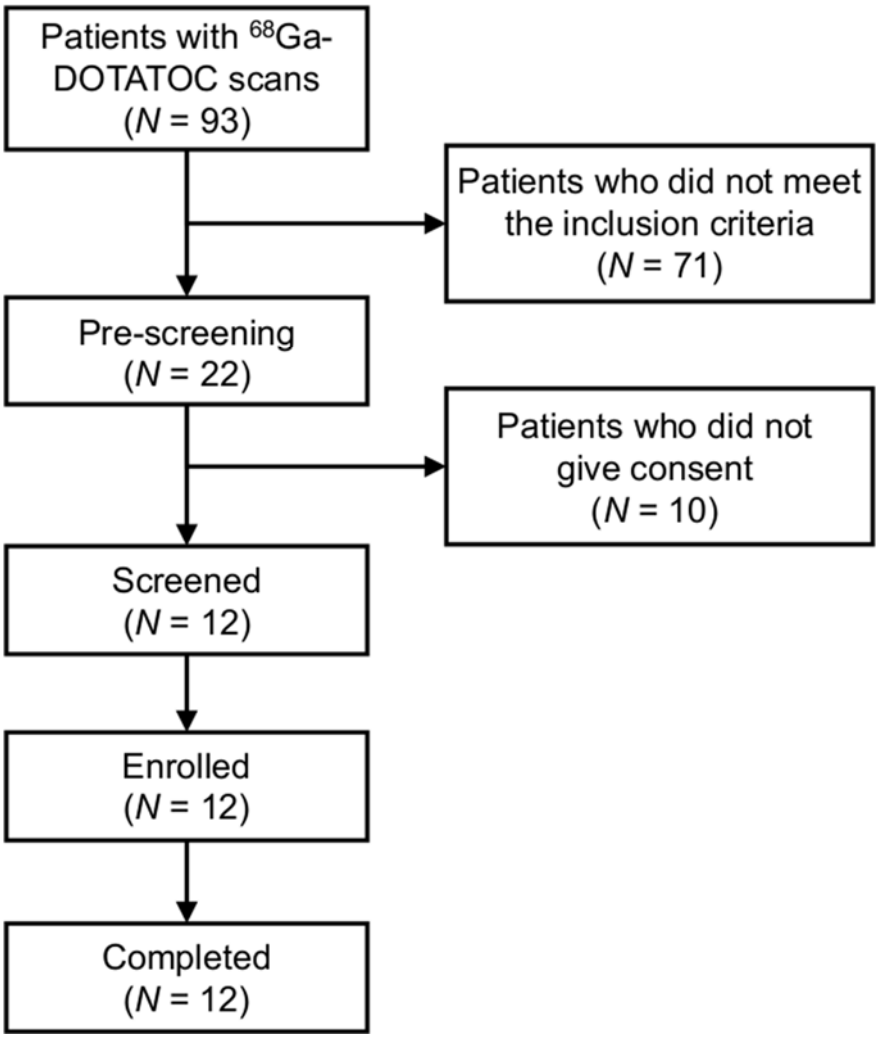

FIGURE 1. Study profile.

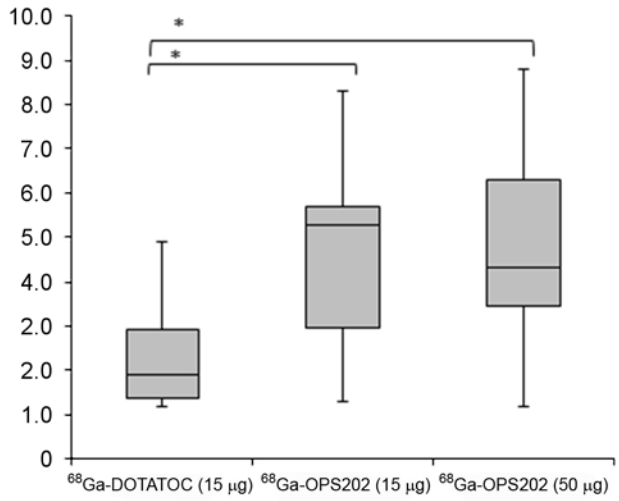

FIGURE 2. Whiskers-box plot representing the tumor-to-liver background uptake ratios of matched liver lesions (median of the mean SUV_{max} ratios, first and third quartile) for both ^{68}Ga-OPS202 scans vs. ^{68}Ga-DOTATOC scan (1 h time point, on-site reader). * In comparison with ^{68}Ga-DOTATOC, both ^{68}Ga-OPS202 scans showed significant increase of the tumor-to-liver background uptake ratio (p=0.004 and 0.008), whilst no statistical difference was shown between the two OPS202 peptide amounts (p=0.547). Note from the sponsor: data listed in this figure are acquired as part of an extension study and are not part of the original study.

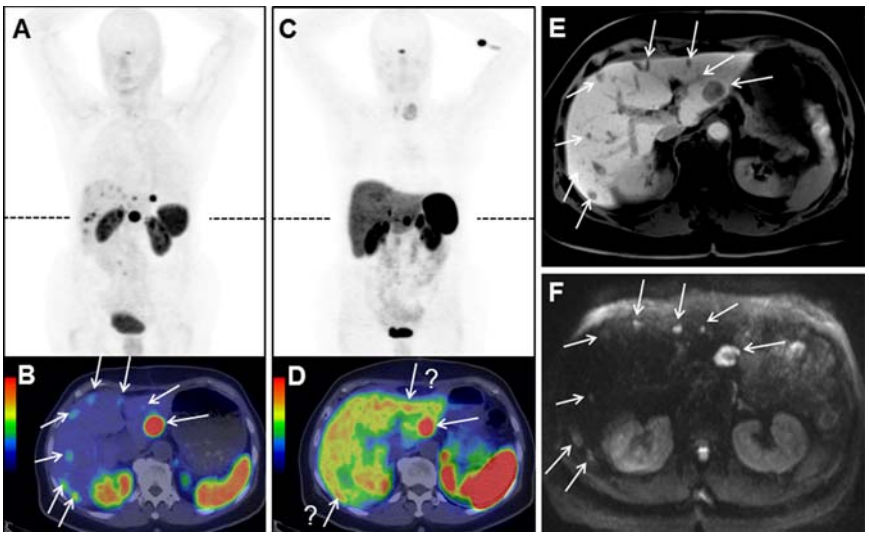

FIGURE 3. ^{68}Ga-OPS202 PET/CT (50 µg) (A, B), ^{68}Ga-DOTATOC PET/CT (C, D) both 1 h post-injection and MRI (E, F) in patient 9 with an ileal NET, showing bilobar liver metastases. Dotted lines show the level of transaxial slices. PET/CT were performed on the same scanner within 2 months and scans were read using the same gray (MIP) and color scale (transaxial fusion). Findings were correlated with liver MRI performed 4 months after ^{68}Ga-OPS202 PET/CT, with delayed post-contrast acquisitions (E) and diffusion weighted images (F), confirming the additional metastases missed or questionable (arrow with question mark) on ^{68}Ga-DOTATOC PET/CT. Importantly, background activity of ^{68}Ga-OPS202 was lower in the liver, intestine and thyroid than with ^{68}Ga-DOTATOC (e.g. for the liver mean SUVmax was 2.6 vs 10.2). Repeated thyroidectomy for benign goiter failed to demonstrate malignancy of the left thyroid nodule.

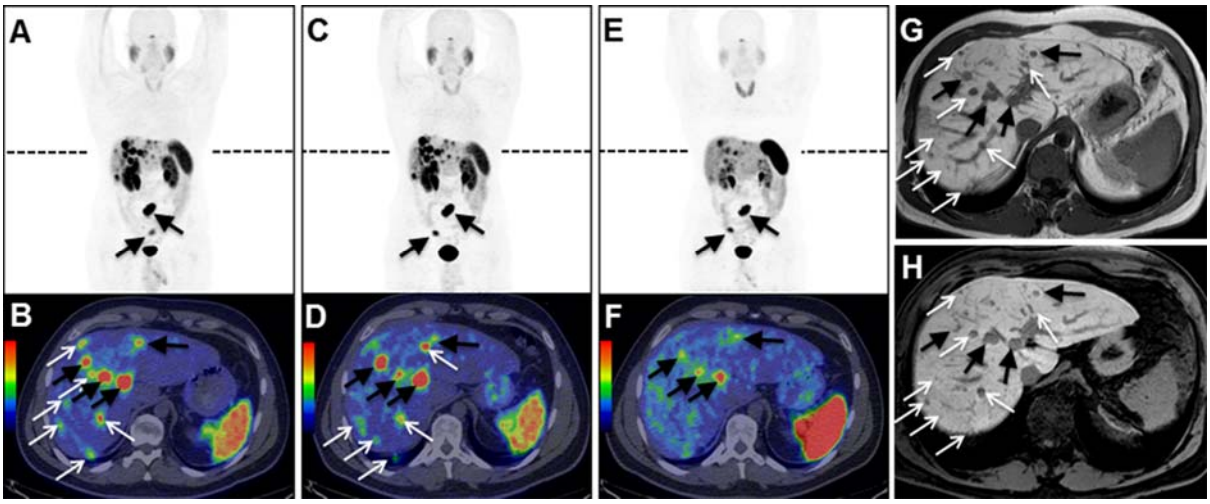

FIGURE 4. ^{68}Ga-OPS202 PET/CT (50 µg) (A, B), ^{68}Ga-OPS202 PET/CT (15 µg) (C, D), ^{68}Ga-DOTATOC PET/CT (15 µg) (E, F) acquired 1 h p.i and MRI scans (G, H) in patient 10 with an ileal NET. Dotted lines show the level of transaxial slices. ^{68}Ga-OPS202 scans are performed 25 and 4 days after ^{68}Ga-DOTATOC PET/CT. Mean liver SUVmax was 4.6 and 4.7 for 15 and 50 µg ^{68}Ga-OPS202 and 5.6 for ^{68}Ga-DOTATOC. While ^{68}Ga-DOTATOC and both ^{68}Ga-OPS202 PET/CT showed the ileal primary, a mesenteric malignant mass and multiple liver metastases (black arrows), ^{68}Ga-OPS202 PET/CT scans detected significantly more liver metastases (white arrows). Head-to-head comparison with MRI performed 7 months after ^{68}Ga-OPS202 scans confirmed the suspicious findings as true positive only on ^{68}Ga-OPS202 PET/CT scans (white arrows).

TABLE 1

Baseline demography and disease characteristics

Patient	Age (years)	Gender	Primary tumor localization	Tumor grade (Ki-67 value)	Hormonal Status	Indication of imaging	Primary tumor resected
1	74	F	Ileum	G1 (<2%)	Functional	Re-staging	yes
2	56	F	Ileum	G1 (<2%)	Functional	Staging	yes
3	45	F	Pancreas	G2 (5%)	Non-functional	Re-staging	yes
4	41	F	Ileum	G1 (1%)	Non-functional	Re-staging	yes
5	56	M	Pancreas	G1 (<2%)	Non-functional	Re-staging	no
6	39	M	Pancreas	G2 (5%)	Non-functional	Re-staging	yes
7	72	M	Ileum	G2 (3 - 5%)	Non-functional	Re-staging	yes
8	67	M	Unconfirmed (midgut)	G1 (<2%)	Functional	Re-staging	yes
9	71	F	Ileum	G2 (NA)	Functional	Re-staging	yes
10	32	M	Ileum	G2 (2 - 5%)	Functional	Re-staging	no
11	63	M	Ileum	G1 (1%)	Non-functional	Re-staging	yes
12	42	M	Pancreas	G1 (<2%)	Non-functional	Re-staging	yes

NA = not available. Hormonal status was defined by either presence of clinical features typical for secretory syndrome (e.g. carcinoid syndrome)

or based on the presence of hormone or their catabolites in the serum or urine.

TABLE 2

Lesion-based comparison of ^{68}Ga-OPS202 PET/CT scans and ^{68}Ga-DOTATOC reference PET/CT scan at one hour

	50 µg ^{68}Ga-OPS202 PET/CT		15 µg ^{68}Ga-OPS202 PET/CT		15 µg ^{68}Ga-DOTATOC PET/CT		p-value*
	On-site Reader	Central Reader	On-site Reader	Central Reader	On-site Reader	Central Reader	
Liver	149	195	151	157	97	77	<0.05
Lymph node	27	20	28	23	27	20	NS
Other sites	20	6	24	7	22	5	NS
Total	196	221	203	187	146	102	<0.05

*Comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT was done separately for on-site and central readers. NS = not significant.

TABLE 3

Organ, tumor and tumor-to-background uptake ratios: ^{68}Ga-OPS202 vs. reference ^{68}Ga-DOTATOC scan (one hour; matched lesion analysis; on-site reader). Note from the sponsor: data listed in this table are acquired as part of an extension study and are not part of the original study design

	^{68}Ga-DOTATOC scan	^{68}Ga-OPS202 scan	
	15 µg	15 µg	50 µg
Normal organ uptake (median SUV_{max}, [interquartile range])			
Liver	6.5 [4.8 - 8.9]	3.4 [2.7 - 3.6] (vs ^{68}Ga-DOTATOC p=0.0005)	2.7 [2.5 - 3.1] (vs ^{68}Ga-DOTATOC p=0.0005)
Pancreas (uncinate process)	3.9 [3.2 - 5.7]	2.2 [2.0 - 3.6] (p=0.0005)	2.2 [2.0 - 2.5] (p=0.001)
Gastro-intestinal tract	5.4 [4.8 - 5.9]	3.4 [2.8 - 3.8] (p=0.001)	2.9 [2.4 - 3.2]* (p=0.0005)
Lung	0.7 [0.6 - 0.9]	1.7 [1.1 - 2.0] (p=0.0005)	1.6 [1.1 - 1.9] (p=0.0005)
Tumor uptake (median of the mean SUV_{max}, [interquartile range])			
Liver lesions	11.8 [10.6 - 14.0]	10.9 [9.5 - 20.7] (p=0.547)	12.6 [9.6 - 19.9] (p=0.652)
Extra-hepatic lesions	14.3 [8.1 - 16.3]	11.8 [7.7 - 14.6] (p=0.641)	10.2 [6.3 - 15.1] (p=0.234)
All lesions	12.4 [12.0 - 14.5]	12.3 [9.9 - 16.9] (p=0.880)	14.4 [9.6 - 16.3] (p=0.966)
Tumor-to-background uptake ratio (median of the mean SUV_{max}, [interquartile range])			
Liver	1.9 [1.4 - 2.9]	5.3 [2.9 - 5.7] (p=0.004)	4.3 [3.4 - 6.3] (p=0.008)

*Significant difference between 15 and 50 µg ^{68}Ga-OPS202 was observed for the physiological uptake (median SUV_{max}) in the intestine (p=0.032). There was a trend regarding the liver and pancreas, close to statistical significance with a p-value of 0.062 and 0.053 respectively. No statistical difference was

observed between 15 and 50 µg ^{68}Ga-OPS202 in terms of tumor uptake for liver, extra-hepatic metastases and overall, or for tumor-to-liver uptake ratio, p=0.359, 0.156, 0.186 and 0.547 respectively.

TABLE 4

Lesion-based comparison of ^{68}Ga-OPS202 PET/CT scans and ^{68}Ga-DOTATOC PET/CT 1 h p.i. Analyses for sensitivity and PPV of on-site and central reading was performed including 95% CI. Note from the sponsor: data listed in this table are acquired as part of an extension study and are not part of the original study design

	50 µg ^{68}Ga-OPS202 PET/CT	15 µg ^{68}Ga-OPS202 PET/CT	15 µg 68Ga-DOTATOC PET/CT	Test for superiority
Sensitivity	93.7% (85.3 - 97.6)	88.1% (74.4 - 95.2)	59.2% (36.3 - 79.1)	p<0.001*
Positive predictive value (PPV)	98.5% (82.8 - 99.9)	98.0% (77.9 - 99.9)	97.8% (76.3 - 99.9)	NS

*Analyses for superiority of 15 or 50 µg ^{68}Ga-OPS202 versus ^{68}Ga-DOTATOC PET/CT were conducted. P-values for comparisons of sensitivities of 15 or 50 µg ^{68}Ga-OPS202 versus ^{68}Ga-DOTATOC PET/CT were both <0.001. Test for superiority regarding PPV could not show significant differences in any of the three comparisons. NS = not significant.