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A randomised, factorial phase II study to determine the optimal dosing regimen for ^{68}Ga-satoreotide trizoxetan as an imaging agent in patients with gastroenteropancreatic neuroendocrine tumours

Running Title: ^{68}Ga-satoreotide trizoxetan optimal dose

Irene Virgolini[1], Shadfar Bahri[2], Andreas Kjaer[3], Henning Grønbæk[4], Peter Iversen[5], Esben A. Carlsen[3], Mathias Loft[3], Ulrich Knigge[6], Johanna Maffey-Steffan[1], Christine Powell[7], Colin G. Miller[8], Thomas Rohban[9], Sandy McEwan[7], and Johannes Czernin[2]

[1]Department of Nuclear Medicine, University of Innsbruck, Innsbruck, Austria; [2]Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, UCLA, Los Angeles, California; [3]Department of Clinical Physiology, Nuclear Medicine & PET and Cluster for Molecular Imaging, Department of Biomedical Sciences, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [4]Department of Hepatology & Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [5]Department of Nuclear Medicine and PET Center, Aarhus University Hospital, Aarhus, Denmark; [6]Department of Endocrinology PE and Department of Surgery C, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [7]Ipsen Bioscience, Cambridge, MA, USA; [8]The Bracken Group for Ipsen Bioscience, Newtown, PA, USA; and [9]Partner 4 Health for Ipsen Bioscience, Paris, France

Corresponding Author: Dr. Irene Virgolini, Department of Nuclear Medicine, University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria. Tel: +43 512 504 82307; E-mail: irene.virgolini@i-med.ac.at.

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ABSTRACT

^{68}Ga-satoreotide trizoxetan is a novel somatostatin receptor antagonist associated with high sensitivity and reproducibility in neuroendocrine tumour (NET) detection and localisation. However, the optimal peptide mass and radioactivity ranges for ^{68}Ga-satoreotide trizoxetan have not yet been established. We therefore aimed to determine its optimal dosing regimen in patients with metastatic gastroenteropancreatic NETs in a prospective, randomised, 2×3 factorial, multicentre, phase II study.

Methods: Patients received ^{68}Ga-satoreotide trizoxetan at a peptide mass of 5–20 µg on day 1 of the study and of 30–45 µg on day 16–22, at one of three gallium-68 radioactivity ranges (40–80, 100–140, or 160–200 MBq). Whole-body PET/CT imaging was performed 50–70 minutes after each injection. The primary endpoint was the detection rate of NET lesions imaged by ^{68}Ga-satoreotide trizoxetan relative to contrast-enhanced CT (CECT) (for each of the six peptide mass/radioactivity range combinations).

Results: Twenty-four patients were evaluated in the per-protocol analysis. The median number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT or PET only was at least twice as high as the number of lesions detected by CECT across the six studied peptide mass dose/radioactivity range combinations. There were no differences between the two peptide mass ranges and between the three radioactivity ranges in the number of identified lesions. However, a trend towards a lower

relative lesion count was noted in the liver for the 40–80 MBq range. No relationship was observed between the radioactivity range per patient's body weight (MBq/kg) and the number of lesions detected by ^{68}Ga-satoreotide trizoxetan. Median diagnostic sensitivity of ^{68}Ga-satoreotide trizoxetan PET/CT, based on the number of lesions per patient, ranged from 85% to 87% across the different peptide mass and radioactivity ranges. Almost all reported adverse events were mild and self-limiting.

Conclusion: A radioactivity of 100–200 MBq with a peptide mass up to 50 μg were confirmed as the optimal dosing regimen for ^{68}Ga-satoreotide trizoxetan to be used in future phase III studies.

Keywords: ^{68}Ga-satoreotide trizoxetan; neuroendocrine tumours; somatostatin receptor antagonist; diagnostic imaging; optimal dose

Word Count: 5,375.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) constitute a heterogeneous group of tumours, most of which overexpress somatostatin receptors (SSTRs) (*1*). The current standard for the diagnosis and staging of NETs is positron emission tomography (PET)/computed tomography (CT) using radiolabelled SSTR2 agonists such as ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, or ^{64}Cu-DOTATATE (*2–4*). The introduction of SSTR2 antagonists represents an important development in the field of NET imaging, as they bind to more receptors than SSTR2 agonists and therefore provide a higher tumour uptake, with better NET visualisation (*5–8*).

^{68}Ga-satoreotide trizoxetan (also known as ^{68}Ga-IPN01070, ^{68}Ga-NODAGA-JR11, or ^{68}Ga-OPS202) is a new generation somatostatin antagonist developed as a PET imaging agent for the detection and localisation of NET lesions. It consists of the small somatostatin analogue JR11 conjugated to the strong cyclical chelating agent 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (NODAGA), which is radiolabelled with the isotope gallium-68. A previous prospective, single-centre, open-label, phase I/II imaging study (*9*), conducted in 12 patients with well-differentiated, low- or intermediate-grade, SSTR2-positive GEP-NETs, found that ^{68}Ga-satoreotide trizoxetan, administered at a peptide mass ranging from 11 to 63 µg and an activity from 125 to 192 MBq, was associated with a significantly higher lesion-based overall sensitivity compared to the SSTR2 agonist ^{68}Ga-DOTATOC (88%–94% versus 59%; $p<0.001$). This observation was mainly attributed to the higher detection rate of metastases in the liver (*9*).

We report on a prospective, multicentre, phase II trial designed to expand on the aforementioned phase I/II study (*9*) by confirming the optimal peptide mass dose and radioactivity ranges for ^{68}Ga-satoreotide trizoxetan in patients with metastatic GEP-NETs. Furthermore, this study was designed based on the United States Food and Drug Administration's request for more

data on the optimal diagnostic performance of ^{68}Ga-satoreotide trizoxetan for PET imaging in a multicentre setting. It was hypothesised that an administered activity range of 40–80 MBq (1.08–2.16 mCi) would provide a reduced diagnostic signal compared to the recommended range of 100–200 MBq (2.70–5.41 mCi).

MATERIALS AND METHODS

Study Design

This open-label, reader-blinded, dose-confirmation, 2×3 factorial, randomised (1:1:1), phase II study (ClinicalTrials.gov identifier: NCT03220217; EudraCT no.: 2016-004928-39) investigated two peptide mass dose ranges (5–20 and 30–45 µg) and three radioactivity ranges (40–80, 100–140, and 160–200 MBq) of ^{68}Ga-satoreotide trizoxetan. The study was prospectively designed to enrol eight patients in each of the three arms to ensure a balanced inter-dose evaluation. Patients all received two doses of ^{68}Ga-satoreotide trizoxetan on two separate visits, 2–3 weeks apart, according to the randomisation schedule of the three arms as shown in Figure 1.

Each patient underwent a total of four visits: a screening visit (visit 1) conducted within two weeks prior to the first ^{68}Ga-satoreotide trizoxetan administration; on day 1 (visit 2) of the study during which all patients received ^{68}Ga-satoreotide trizoxetan at a peptide mass of 5–20 µg with one of the three gallium-68 radioactivity ranges (40–80 MBq, arm A; 100–140 MBq, arm B; or 160–200 MBq, arm C); on day 16–22 (visit 3) during which patients received the second dose of ^{68}Ga-satoreotide trizoxetan at 30–45 µg and a different radioactivity range than the one administered on day 1; and an end-of-study visit (visit 4) on day 30–36 of the study for safety evaluation.

At screening, patient information was collected including medical and surgical history, the primary tumour site, tumour grade, histopathology, and PET images demonstrating SSTR2-expressing lesions obtained within the previous six months. A physical examination including vital sign assessment and laboratory tests (including haematology, blood chemistry, and urinalysis) were performed at all study visits. A 12-lead electrocardiogram was recorded at screening and at the end-of-study.

The study was conducted between September 2017 and October 2019 at four investigational sites in Austria, Denmark, and the United States. It was approved by all relevant ethics committees, and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline on Good Clinical Practice. All patients provided written informed consent, and data were anonymised.

Patients

Adults with pathologically confirmed, well-differentiated, functioning or non-functioning, metastatic grade 1/2 GEP-NETs were enrolled in this study. All patients had to have ≥2 and ≤25 lesions/organ expressing SSTR2, which were identified with prior SSTR2 agonist PET scans in either the primary tumour site or in key organs (liver, lymph nodes, bones and lungs). The limits were to ensure that a total number of lesions could be counted for statistical evaluation. Patient admissibility based on the number of SSTR2-expressing lesions was confirmed centrally by an independent nuclear medicine physician. Other inclusion criteria were: an Eastern Cooperative Oncology Group performance status of 0–2, a body weight of 50–110 kg, and adequate hepatic, renal, and haematologic functions.

Key exclusion criteria were treatment with short- or long-acting somatostatin analogues within 24 hours or 28 days, respectively, before either ^{68}Ga-satoreotide trizoxetan injection, and any condition that might preclude the acquisition of high-quality PET and/or CT images.

Imaging

At each of the four study centres, whole-body PET imaging was performed at both visit 2 and visit 3 of the study 50–70 minutes post-intravenous injection of ^{68}Ga-satoreotide trizoxetan,

using Siemens Biograph dedicated PET/CT scanners, with an acquisition time of 2–4 minutes per bed position. All PET scans were acquired in list mode, including time-of-flight capability. Whole-body, low-dose CT images were acquired for localisation and attenuation correction. During the same visits, patients also underwent contrast-enhanced CT (CECT) imaging, performed independently on a dedicated CT scanner and used as the standard-of-truth.

All images, including the pre-screening SSTR agonist images, were sent to an imaging core lab (Keosys, Nantes, France) after anonymisation. Following quality control, the images were reviewed on a dedicated workstation. The PET images with and without the CT scans were evaluated by two experienced nuclear medicine physicians and one adjudicator for discordant cases. In parallel, CECT scans were read by two other radiologists, with a third adjudicating discordances. To minimise bias, the independent readers were blinded to patient data, any information related to the study site, injected dose, and the temporal sequence of images.

Radiopharmaceutical

^{68}Ga-satoreotide trizoxetan was prepared at the study centre's local radiopharmacy, using the clinical trial dose kit provided by Beaufour Ipsen Industries (Dreux, France), by a two-step aseptic compounding process. This process included: 1) reconstitution of the sterile vial A containing the satoreotide trizoxetan precursor and excipients with 1 mL of the solvent consisting of a solution of sterile sodium acetate from vial B; 2) radiolabelling of satoreotide trizoxetan by the addition of a 5-mL sterile hydrochloric acid solution of gallium-68, eluted from a sterile pharmaceutical grade germanium-68/gallium-68 generator (Eckert & Ziegler Radiopharm, Berlin, Germany).

The total amount of radioactivity (MBq) injected by a slow push intravenous injection into each patient was determined by measuring the radioactivity in the syringe before and after injection, using a standard dose calibrator. The peptide dosage corresponded to injected volume (mL) x 8.33 µg/mL.

Efficacy Assessments

All efficacy endpoints were assessed in the primary tumour site and in key organs (liver, lymph nodes, lungs, and bones), and were also evaluated in quartiles of radioactivity per baseline body weight expressed as MBq/kg. The primary endpoint of the study was the ratio of the number of lesions detected by a) ^{68}Ga-satoreotide trizoxetan PET/CT and b) PET alone, to the number of lesions identified by CECT scan, for each of the six peptide mass dose/radioactivity range combinations. CECT was used as the standard-of-truth to provide a standardised denominator in order to make valid comparisons by peptide mass and radioactivity range.

Secondary efficacy endpoints included: mean and median tumour-to-background ratios calculated by radioactivity range per patient's body weight; preliminary diagnostic sensitivity of ^{68}Ga-satoreotide trizoxetan PET/CT based on the number of lesions per patient compared to the standard-of-truth; and the absolute number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT and the difference with the number of lesions detected by CECT scan. Preliminary diagnostic sensitivity was calculated as the number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT and CECT scan / (number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT and CECT scan + number of lesions detected by CECT scan but not by ^{68}Ga-satoreotide trizoxetan PET/CT).

Safety Assessments

The safety and tolerability of ^{68}Ga-satoreotide trizoxetan were assessed throughout the study on the basis of adverse events (AEs) which were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and coded using the Medical Dictionary for Regulatory Activities (version 22.1), laboratory results (haematologic, biochemical, and urologic), physical examinations, vital signs, and electrocardiography.

Statistical Analysis

Statistical analysis was descriptive; consequently, no formal sample size calculation was performed. Continuous variables were presented as mean, standard deviation, median, and range, whereas categorical variables were described by counts and percentages. The safety population was defined as all patients who received at least one dose of ^{68}Ga-satoreotide trizoxetan. By contrast, in order to ensure a balanced and adequate assessment for each dosage regimen, only the first eight patients in each arm who successfully completed all ^{68}Ga-satoreotide trizoxetan PET/CT scans were used in the efficacy analysis and were consequently included in the per-protocol population.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Missing values were not replaced.

RESULTS

Patients

A total of 29 patients were enrolled in the study, with a median age of 63.0 years (Table 1). Two patients withdrew from the study before receiving ^{68}Ga-satoreotide trizoxetan, leaving 27 patients in the safety population (arm A, n=8; arm B, n=9; arm C, n=10), as illustrated in Figure 2. The per-protocol population consisted of 24 patients (n=8 per arm) as initially planned.

Baseline demographic and disease characteristics were overall well-balanced between the three study arms, with the small intestine being the most frequent primary tumour site and liver and lymph nodes the most frequent metastasis locations (Table 1; Table 2). Overall, 28 out of the 29 (96.6%) patients received at least one prior treatment, including somatostatin analogues in 26 (89.7%) patients, ^{177}Lu-DOTATATE in 17 (58.6%), and everolimus in 3 (10.3%) patients. There were no intercurrent treatments reported between radiolabelled SSTR agonists and antagonists or between two consecutive SSTR antagonists at any time of the study in any patient.

All 24 patients in the per-protocol population had a prior SSTR scan performed within a median of 1.6 months (range, 0.1–6.0 months) from screening: 14 (58.3%) had a PET/CT scan with ^{68}Ga-DOTATOC, 9 (37.5%) with ^{64}Cu-DOTATATE, and 1 (4.2%) with ^{68}Ga-DOTATATE. The median (range) total number of SSTR-positive lesions detected by prior SSTR agonist scans was 14.5 (6.0–94.0). The median (range) number of positive SSTR-lesions was 1.0 (0–1.0) in the primary tumour site, 9.5 (0–37.0) in the liver, 5.0 (0–36.0) in the lymph nodes, and 0.5 (0–38.0) in the bones. Three patients were enrolled with >30 lesions identified in the liver or in the lymph nodes.

Efficacy

For all organs combined, the median number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT or PET only was at least twice as high as the number of lesions detected by CECT across the six peptide mass dose/radioactivity range combinations. This was reflected by a median relative lesion count, i.e., the ratio of the number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT or PET only to the number of lesions detected by CECT, ranging from 2.1 to 3.9. The results for the primary efficacy endpoint are shown in Table 3. When comparing the two administered peptide mass ranges as well as the three radioactivity ranges of ^{68}Ga-satoreotide trizoxetan, there was no specific distribution pattern in the median relative lesion count for all organs combined. However, a trend towards a lower median relative lesion count in the liver was noted for the 40–80 MBq range compared to the higher radioactivity ranges (Table 3). When counting the number of lesions detected by ^{68}Ga-satoreotide trizoxetan imaging in each of the three study arms, there was exact agreement among the two readers for all patients in arm B (100%), whereas the inter-reader agreement rate was 87.5% in arm A and 75% in arm C.

Similarly, no pattern indicating a possible association between the radioactivity range per patient's body weight (MBq/kg) and the relative lesion count or the absolute number of lesions detected by ^{68}Ga-satoreotide trizoxetan was found (Table 4). There was also no observed association between the radioactivity range per patient's weight with the tumour-to-background ratio (Table 5).

Preliminary diagnostic sensitivity of ^{68}Ga-satoreotide trizoxetan PET/CT, using CECT as the standard-of-truth, ranged from a median of 85% to 87% across different peptide mass dose and radioactivity ranges (Table 6).

Safety

All patients included in the safety population (n=27) received two injections of ^{68}Ga-satoreotide trizoxetan during the study. A total of 33 AEs were reported in 18 patients (66.7%), classified as grade 1 (23 AEs in 15 patients), grade 2 (9 in 5) and grade 3 (1 in 1), the latter event being hypertriglyceridaemia. Overall, 14 drug-related AEs were reported in 7 patients (25.9%), all grade 1 or 2, which included injection site pain (4 events), nausea (2 events), proteinuria (2 events), feeling cold (2 events), flushing (1 event), alopecia (1 event), diarrhoea (1 event), and fatigue (1 event). Drug-related AEs occurred 1–2 days after the last dose of ^{68}Ga-satoreotide, and were resolved within 15 days. Patients completely recovered from all drug-related AEs, except for one patient with reported alopecia that recovered with sequelae. No serious AEs and no post-dose AEs leading to withdrawal or death were reported.

DISCUSSION

This multicentre, randomised, factorial phase II study evaluated the optimal dose range of ^{68}Ga-satoreotide trizoxetan. The results showed that the ratio of the number of lesions detected by ^{68}Ga-satoreotide trizoxetan to the number of lesions detected by CECT was overall consistent across different peptide mass and radioactivity ranges, with no dependence on subject weight; however, a lower relative lesion count (median) in the liver was noted for the 40–80 MBq range compared to the higher radioactivity ranges. As anticipated with radiolabelled somatostatin analogues, the number of lesions identified by ^{68}Ga-satoreotide trizoxetan was consistently higher than that identified by CECT in organs where lesions were present.

For the routine clinical setting, PET/CT images should be considered the primary evaluation in NET patients (*10*,*11*). The primary efficacy analysis found that, with ^{68}Ga-satoreotide trizoxetan PET/CT scans (and also PET alone), there were no noticeable differences between the two peptide masses in the number of identified lesions for all organs, with a median relative lesion count of 2.7 for both peptide mass ranges. Hence, based on the results of primary and secondary endpoints, ^{68}Ga-satoreotide trizoxetan imaging was not peptide mass-dependent. This is corroborated by the phase I/II imaging study by Nicolas et al. (2018) (*9*) which found no significant differences between two administered peptide mass doses (14 ± 4 and 50 ± 15 µg) in the number of malignant liver or lymph node lesions detected per patient or the tumour-to-background ratios, indicating a high reproducibility for ^{68}Ga-satoreotide trizoxetan PET/CT, regardless of the administered amount of peptide. Thereby, the present study, along with the findings of the Nicolas et al. study (*9*), confirms that the optimal peptide mass of ^{68}Ga-satoreotide trizoxetan for the diagnostic imaging of GEP-NETs can be up to 50 µg, which is congruent with the current European Association of Nuclear Medicine administration guidelines for ^{68}Ga-labelled SSTR2 agonists (*10*).

Regarding the optimal administered radioactivity of ^{68}Ga-satoreotide trizoxetan, the present study confirms that the radioactivity ranges of 100–140 and 160–200 MBq provide optimal imaging results. By contrast, the 40–80 MBq radioactivity range is associated with a trend towards a lower median relative lesion count in the liver, the predominant site of metastases in patients with GEP-NETs (*12*), and, therefore, further development will not be pursued for this radioactivity range, which of note was not tested in prior studies. The 40–80 MBq radioactivity range might also be associated with a reduced ratio of receptor-bound tracer to free tracer, resulting in declined image contrast and poor detection of GEP-NETs (*13*,*14*).

The absence of notable diagnostic performance and safety differences between the radioactivity ranges of 100–140 and 160–200 MBq, when discounting the 40–80 MBq range, provides confirmation of the optimal radioactivity range and ascertains the 100–200 MBq range as the appropriate activity for future use of ^{68}Ga-satoreotide trizoxetan. This is in keeping with the European Association of Nuclear Medicine guidelines which recommend an administered radioactivity range of ^{68}Ga-labelled SSTR2 agonists between 100 and 200 MBq, depending on the technical characteristics of the PET scanner and the patient's body weight (*10*). Similarly, the Society of Nuclear Medicine and Molecular Imaging recommends administration of ^{68}Ga-labelled SSTR2 agonists at a radioactivity between 111 and 259 MBq, while taking into account the patient's body weight (*11*). Although there is a possibility of narrowing the radioactivity window of ^{68}Ga-satoreotide trizoxetan from 100–200 to 100–140 MBq, adopting the wider, guideline-recommended radioactivity range of 100–200 MBq offers increased flexibility and feasibility in routine clinical practice, while maintaining similarity in dosing to other gallium-68-labelled products. The absence of a clear dose-response relationship in the present study might be related to factors such as

heterogeneity in receptor density, hypoxia, interstitial pressure, necrosis, and tumour heterogeneity (*15*).

Of significant note, this study did not find a weight-dependent effect of ^{68}Ga-satoreotide trizoxetan across the evaluated quartiles of radioactivity (MBq)/body weight (kg). This ideally provides the opportunity for an activity range of ^{68}Ga-satoreotide trizoxetan (100–200 MBq) to be prescribed, regardless of body weight. By contrast, ^{68}Ga-labelled SSTR2 agonists require dosing per body mass (*10,11,16*). In a recent prospective study from the Netherlands conducted among 21 patients with NETs who underwent whole-body ^{68}Ga-DOTATATE PET/CT, Cox and colleagues reported that, of all patient-dependent parameters, body mass showed the strongest correlation (coefficient of determination of 0.60) with normalised signal-to-noise ratio (*16*). Importantly, the absence of a weight-dependent effect represents a practical advantage for ^{68}Ga-satoreotide trizoxetan, as an administered activity within a predetermined range instead of a weight-based administered activity is not only more convenient but also reduces the possibility of dosing errors.

The frequency and nature of the AEs reported with ^{68}Ga-satoreotide trizoxetan in the present study did not raise any safety concern. Of note, many of these clinical manifestations (e.g., nausea, flushing, diarrhoea, fatigue) are common in patients with NETs. This compares favourably with the safety profile in the Nicolas et al. (2018) imaging study (*17*), in which no severe AEs or post-dose AEs leading to withdrawal or death were reported.

This study is mainly limited by a small sample size, which negated the use of a formal statistical analysis; thus, descriptive statistical analyses were applied. In addition, while not affecting image readability, the enrolment of three patients with >25 lesions/organ did increase lesion burden and skewed distributions in some instances. The study was also designed to evaluate five different organs (primary tumour site, liver, lymph nodes, lungs, and bones). However, due to

the few lesions identified in certain organs, meaningful results regarding the number of identified lesions were only available for all organs combined, the liver, and lymph nodes. Nevertheless, these limitations were balanced by a robust study design that allowed inter- and intra-individual comparisons across different peptide mass and radioactivity range combinations, which were evaluated at patient and lesion levels for both ^{68}Ga-satoreotide trizoxetan PET/CT and PET only.

CONCLUSION

The overall results of this study confirm an optimal administered peptide mass of ^{68}Ga-satoreotide trizoxetan up to 50 μg with a radioactivity of 100–200 MBq, which is in line with current guidelines for administration of ^{68}Ga-labelled radiopharmaceuticals (*10*,*11*). This phase II study also confirmed that the overall safety profile of ^{68}Ga-satoreotide trizoxetan is acceptable for continued clinical development.

DISCLOSURE

This study was funded by Ipsen (Boulogne, France). IV has acted as a consultant for Ipsen and Advanced Accelerator Applications. HG serves on the advisory board of Ipsen. CGM has acted as a consultant for Ipsen, CytoSite Bio and Alacrita, and is a managing partner at the Bracken Group. TR is a managing partner at Partner 4 Health, and has acted as a consultant for Ipsen. SM and CP are employees at Ipsen Bioscience. No other conflict of interest exists.

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AUTHOR CONTRIBUTIONS

TR and CGM designed the study. IV, SB, AK, HG, PI, UK, EAC, ML, JMS, and JC performed the experiments. CP, CGM, TR, and SM analysed the data. IV, AK, HG, JC, CGM, and TR supervised the study. All authors reviewed and edited the manuscript. All authors read and approved the final manuscript.

KEY POINTS

Question: What are the optimal peptide mass and radioactivity ranges for ^{68}Ga-satoreotide trizoxetan administered as a PET imaging agent in patients with GEP-NETs?

Pertinent Findings: In this prospective, randomised, open-label, factorial-design, phase II study, the ratio of the number of lesions detected by ^{68}Ga-satoreotide trizoxetan to the number detected by CECT was overall consistent across different peptide mass and radioactivity ranges, with no weight-dependent effect. However, a radioactivity range of 40–80 MBq was associated with a trend towards a lower median relative lesion count in the liver, the predominant site of metastasis in patients with GEP-NETs.

Implications for Patient Care: A radioactivity of 100–200 MBq with a peptide mass up to 50 μg were confirmed as the optimal dosing regimen for ^{68}Ga-satoreotide trizoxetan to be used in future phase III clinical trials.

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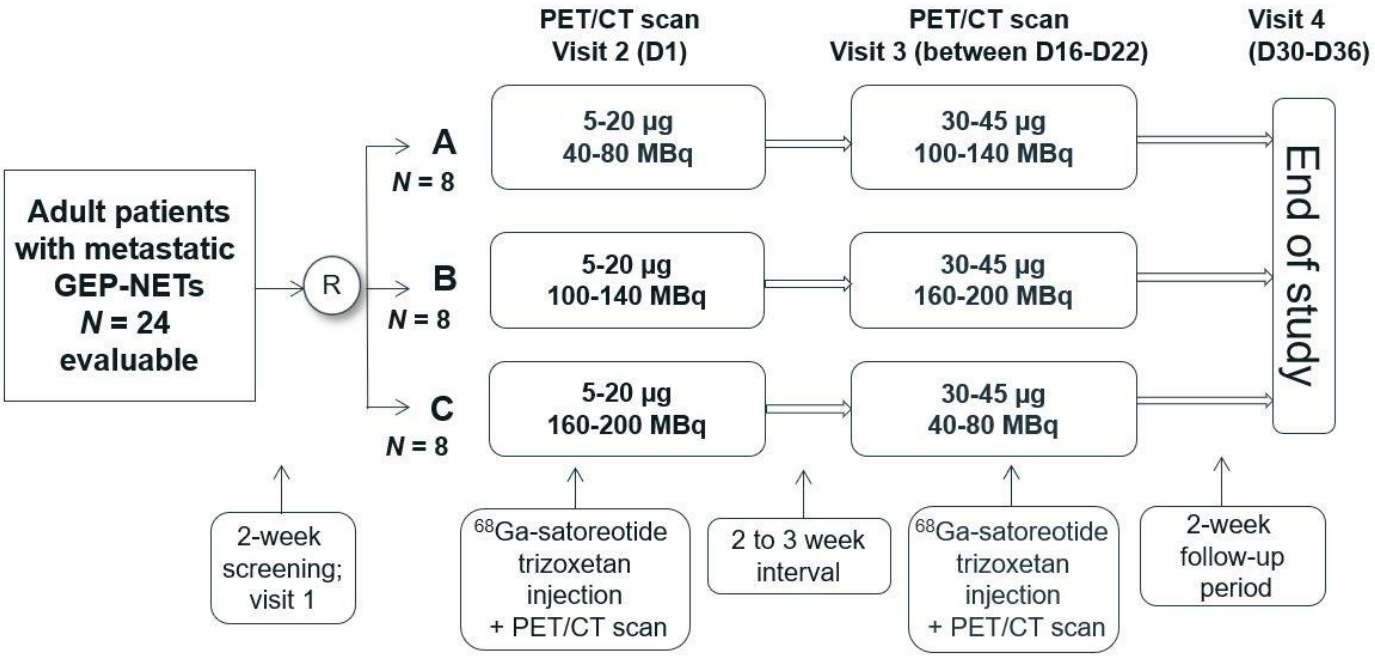

Figure 1. Study design. Abbreviations: CT, computed tomography; D, day; GEP, gastroenteropancreatic; NET, neuroendocrine tumour; PET, positron emission tomography; R, randomised.

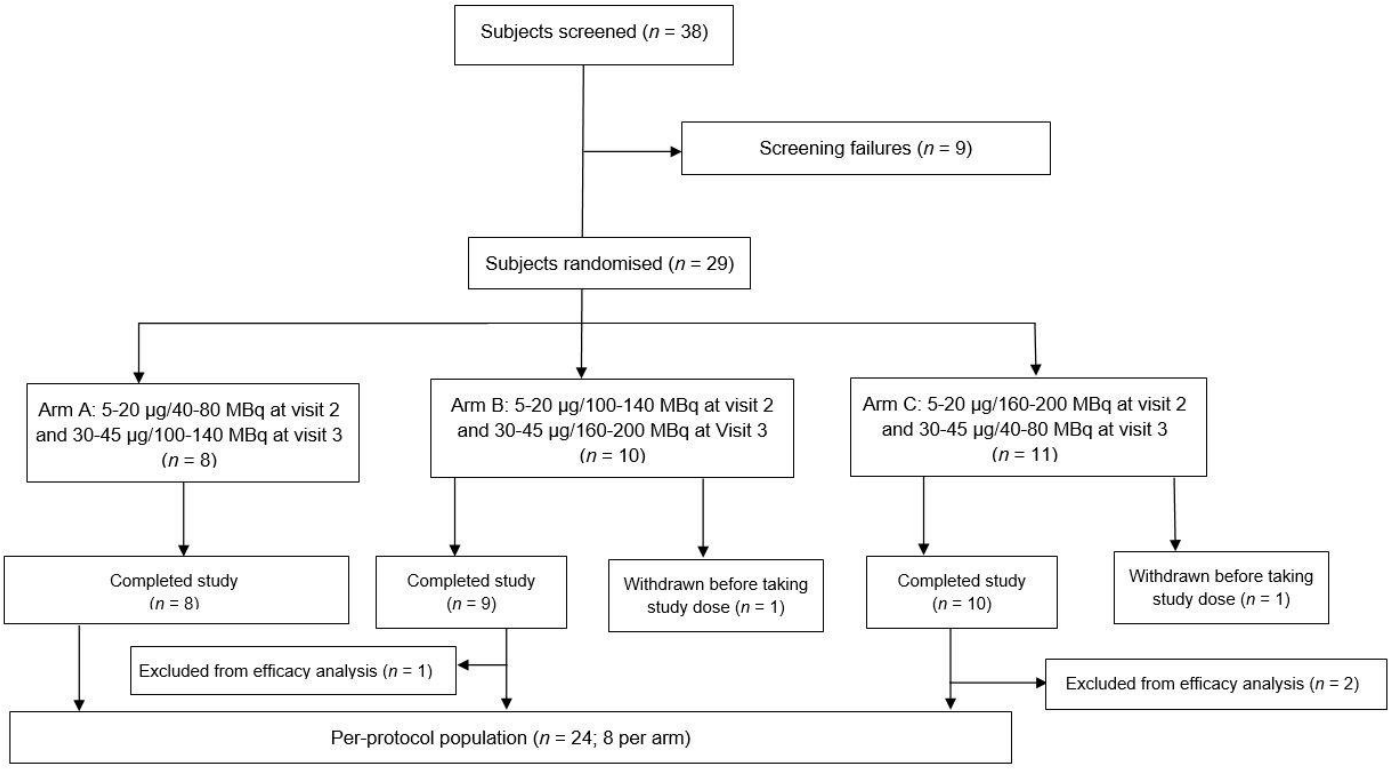

Figure 2. Patient disposition

TABLE 1

Baseline Demographic Characteristics in the Randomised Population

Parameter	**Arm A (N=8)**	**Arm B (N=10)**	**Arm C (N=11)**	**Overall (N=29)**
Age (years)				
Median [range]	71.5 [54–84]	69.5 [60–78]	59.0 [36–78]	63.0 [36–84]
Sex				
Male	6 (75.0)	4 (40.0)	9 (81.8)	19 (65.5)
Female	2 (25.0)	6 (60.0)	2 (18.2)	10 (34.5)
Weight (kg)				
Median [range]	81.0 [77–98]	85.3 [52–109]	86.0 [56–106]	83.0 [52–109]
BMI (kg/m^2)				
Median [range]	26.4 [24–35]	28.8 [21–34]	26.3 [18–40]	26.4 [18–40]
ECOG performance status				
0	7 (87.5)	8 (80.0)	9 (81.8)	24 (82.8)
1	1 (12.5)	2 (20.0)	2 (18.2)	5 (17.2)

Data presented as n (%), unless otherwise specified. Percentages are calculated as n/N.

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

TABLE 2

Baseline Disease Characteristics in the Per-Protocol Population

Parameter	**Arm A (N=8)**	**Arm B (N=8)**	**Arm C (N=8)**	**Overall (N=24)**
Site of primary tumour				
Small intestine	6 (75.0)	4 (50.0)	6 (75.0)	16 (66.7)
Pancreas	1 (12.5)	1 (12.5)	1 (12.5)	3 (12.5)
Large intestine	1 (12.5)	3 (37.5)	1 (12.5)	5 (20.8)
Location of metastasis				
Liver	8 (100.0)	6 (75.0)	8 (100.0)	22 (91.7)
Lymph nodes	5 (62.5)	8 (100.0)	6 (75.0)	19 (79.2)
Bones	2 (25.0)	1 (12.5)	2 (25.0)	5 (20.8)
Lungs	2 (25.0)	0	2 (25.0)	4 (16.7)

Data presented as n (%). Percentages are calculated as n/N.

TABLE 3

Relative Lesion Count in the Per-Protocol Population (N=24), by Peptide Mass and Radioactivity Ranges

	All organs*		**Liver**		**Lymph nodes**	
	PET/CT	**PET**	**PET/CT**	**PET**	**PET/CT**	**PET**
Peptide mass range						
5–20 µg	n=24 2.7 (0.64–16.25)	n=24 2.6 (0.73–19.00)	n=17 2.3 (0.73–9.00)	n=17 2.6 (0.67–7.00)	n=13 2.0 (0.00–8.00)	n=13 2.3 (0.50–10.00)
30–45 µg	n=24 2.7 (0.82–13.50)	n=24 2.8 (0.68–14.50)	n=17 3.0 (0.76–11.00)	n=17 2.8 (0.62–9.00)	n=13 1.3 (0.00–12.00)	n=13 2.0 (0.50–14.00)
Radioactivity range						
40–80 MBq	n=16 3.1 (0.73–15.00)	n=16 2.6 (0.68–19.00)	n=13 2.2 (0.73–9.00)	n=13 2.6 (0.62–6.00)	n=7 2.0 (1.00–3.00)	n=7 2.7 (0.75–4.00)
100–140 MBq	n=16 2.6 (0.64–13.50)	n=16 2.8 (1.00–14.50)	n=9 3.0 (0.83–8.00)	n=9 3.3 (0.67–7.00)	n=9 1.3 (0.00–8.00)	n=9 2.0 (0.50–10.00)
160–200 MBq	n=16 2.6 (0.82–16.25)	n=16 2.7 (0.91–13.50)	n=12 2.7 (0.86–11.00)	n=12 2.8 (0.86–9.00)	n=10 1.3 (0.00–12.00)	n=10 2.2 (0.50–14.00)

Data are presented as median (range).

*All organs refer to the primary tumour site + key organs (liver, lymph nodes, lungs, and bones).

Relative lesion count = number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT or PET only / number of lesions detected by contrast-enhanced CT scan.

For the liver and lymph nodes, the number of analysed patients were those who had ≥2 lesions detected by contrast-enhanced CT on the given organ.

Abbreviations: CT, computed tomography; PET, positron emission tomography.

TABLE 4

Overall Lesion Count in the Per-Protocol Population (N=24), by Radioactivity Range (MBq) per Patient's Baseline Body Weight (kg)

	0.69–0.97 MBq/kg (N=14)	**0.97–1.55 MBq/kg (N=10)**	**1.55–2.09 MBq/kg (N=13)**	**2.09–3.72 MBq/kg (N=11)**
Relative lesion count				
Mean ± SD	4.3 ± 4.04	2.9 ± 1.88	3.6 ± 3.31	4.0 ± 4.15
Median (range)	3.5 (0.73–15.00)	2.5 (0.64–7.00)	2.1 (0.82–13.50)	2.6 (1.67–16.25)
Absolute number of detected lesions				
Mean ± SD	26.9 ± 25.95	18.1 ± 20.62	25.9 ± 21.45	26.8 ± 18.59
Median (range)	16.5 (7–94)	11.5 (6–75)	20.0 (8–73)	19.0 (10–65)

Overall relative lesion count = number of lesions detected by ^{68}Ga-satoreotide trizoxetan in all organs / number of lesions detected by contrast-enhanced computed tomography.

The absolute number of detected lesions corresponds here to the absolute number of lesions detected by ^{68}Ga-satoreotide trizoxetan in all organs.

Abbreviation: SD, standard deviation.

TABLE 5

Tumour-To-Background Ratio for the Liver and the Lymph Nodes in the Per-Protocol Population (N=24), by Radioactivity Range (MBq) per Patient's Baseline Body Weight (kg)

Organ		**0.69–0.97 MBq/kg (N=14)**	**0.97–1.55 MBq/kg (N=10)**	**1.55–2.09 MBq/kg (N=13)**	**2.09–3.72 MBq/kg (N=11)**
Liver	n*	11	6	9	8
	Mean ± SD	7.1 ± 5.90	4.3 ± 1.03	4.9 ± 2.95	6.2 ± 3.68
	Median (range)	4.3 (3.07–22.48)	4.0 (3.35–6.13)	4.1 (2.13–10.75)	5.1 (2.57–12.63)
Lymph nodes	n*	5	6	7	8
	Mean ± SD	10.1 ± 7.25	8.3 ± 5.18	9.2 ± 5.16	5.1 ± 3.17
	Median (range)	7.4 (3.53–18.69)	5.3 (4.47–16.10)	11.4 (2.87–15.00)	4.5 (1.54–11.65)

*n corresponds to the number of patients with lesions in either the liver or the lymph nodes. The number of patients with lesions in the primary tumour site and bones was too small (≤3 in each category) to allow a meaningful interpretation.

Abbreviation: SD, standard deviation.

TABLE 6

Preliminary Diagnostic Sensitivity (%) of ^{68}Ga-Satoreotide Trizoxetan PET/CT in the Per-Protocol Population (N=24), by Peptide Mass Dose and Radioactivity Range

	Peptide mass dose range		**Radioactivity range**				
	5–20 µg (N=24)	**30–45 µg (N=24)**	**40–80 MBq (N=16)**	**100–140 MBq (N=16)**	**160–200 MBq (N=16)**	**100–200 MBq (N=24)**	**40–200 MBq (N=24)**
Mean ± SD	79 ± 24	78 ± 28	86 ± 14	71 ± 34	77 ± 25	75 ± 29	80 ± 24
Median (range)	85 (8–100)	87 (0–100)	87 (64–100)	85 (0–100)	86 (8–100)	85 (0–100)	85 (8–100)

Diagnostic sensitivity = number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT and by contrast-enhanced CT scan / (number of lesions detected by ^{68}Ga-satoreotide trizoxetan PET/CT and by contrast-enhanced CT scan + number of lesions detected by contrast-enhanced CT scan but not ^{68}Ga satoreotide trizoxetan PET/CT) x 100.

Abbreviations: CT, computed tomography; PET, positron emission tomography; SD, standard deviation.

Graphical Abstract