Safety, tolerability and clinical implementation of 'ready-to-use' 68gallium-DOTA0-Tyr3-octreotide (68Ga-DOTATOC) (SomaKIT TOC) for injection in patients diagnosed with gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

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ABSTRACT

Background 68Ga-DOTA0-Tyr3-octreotide (68Ga-DOTATOC) positron emission tomography–CT (PET-CT) has superior diagnostic performance compared to the licensed tracer OctreoScan single photon emission CT–CT in patients with gastroenteropancreatic neuroendocrine tumours (GEP-NETs). A new preparation of 68Ga-DOTATOC using a new 'ready-to-use' 68Ga-DOTATOC formulation for injection has been developed (68Ga-DOTATOC (SomaKIT TOC)).

Objectives This study aimed to assess the safety and tolerability of 68Ga-DOTATOC (SomaKIT TOC) and evaluate the feasibility and robustness of implementing it in a NET clinical imaging service.

Methods A first-in-human phase I/II multicentre, open-label study of a single dose of 68Ga-DOTATOC (SomaKIT TOC) 2 MBq/kg±10% (range 100–200 MBq) in patients with biopsy-proven grade 1–2 GEP-NETs. PET-CT was performed post injection. Patients were followed up for 28 days. We next implemented this new synthesis methodology in a clinical service assessed over 11 months.

Results Twenty consenting patients were recruited; 14 males, 6 females; mean (SD) age 58 years (12); NET grade 1 (70%), grade 2 (30%); and 75% with stage IV disease. Twelve patients experienced at least one adverse event (AE) during the study with no grade 3–4 toxicities. Only four AEs were classified as possibly (headache (n=1; 4%), nausea (1; 4%)) or probably (dysgeusia (1; 4%), paraesthesia (1; 4%)) related to the study preparation. One hundred thirteen vials of 68Ga-DOTATOC (SomaKIT TOC) were synthesised with the 'kit' over a period of 11 months for clinical utility. Only 2/113 vials (1.77%) were rejected.

Conclusions The new ready-to-use preparation of 68Ga-DOTATOC (SomaKIT TOC) for injection was safe and well tolerated. This has led to the world's first (EMA) licensed 68Ga-DOTATOC (SomaKIT TOC) radiopharmaceutical for the utility of PET imaging in patients with NETs. This preparation can be robustly implemented into routine clinical practice.

Key questions

What is already known about this subject?

► Staging and assessment of patients with neuroendocrine tumour (NET) is markedly improved with somatostatin receptor imaging especially in patients with NET of grades 1 and 2. OctreoScan (somatostatin receptor scintigraphy (SRS)) has been the predominant licensed tracer to image these tumours until recently. The development of somatostatin positron emission tomography (PET) tracers has further improved the sensitivity and specificity of the somatostatin imaging performing better than SRS, which has led to significant changes in the patients' management pathway. However, these somatostatin PET tracers until now have been unlicensed tracers with differing synthesis methodologies.

What does this study add?

► This is a phased safety and tolerability prospective study using a simplified methodology to synthesise somatostatin PET tracer 68Ga-DOTA0-Tyr3-octreotide (68Ga-DOTATOC) using a 'kit' which also standardises the production of this tracer. This is a first in man safety and tolerability study. It was then implemented into clinical practice.

How might this impact on clinical practice?

► Following the results of this first in human study, the EMA approved the kit product making this the first in the world licensed 68Ga-DOTATOC PET tracer. We then successfully implemented this new synthesis methodology into our routine clinical practice. This licensed product will increase the availability of this tracer to patients safely with a standardised approved production methodology, hence, improving the clinical management of future patients with NET.

INTRODUCTION

The incidence of neuroendocrine neoplasms (NENs) has increased over several decades.[1] NEN constitutes a heterogeneous group of malignancies originating from cells of the endocrine (hormonal) and nervous systems. These entities may be functioning or non-functioning, and differentiation from other types of malignancies is based on pathological findings.[2] Well-differentiated, grade 1 and grade 2 NENs are commonly referred to as neuroendocrine tumours (NETs) as per WHO 2010 classification,[3] and this term will be used for the purpose of the present study.

A unique feature of NETs is somatostatin receptor (SSTR) overexpression on the cell membrane, which make SSTRs a suitable molecular target for specific diagnostic and therapeutic ligands.[4] Grade 1 and 2 NETs[3 5 6] are more sensitive to SSTR imaging.[7]

Historically, the majority of NETs have been investigated by indium-111 (^{111}In)-pentetreotide (OctreoScan), which was the only approved agent for the scintigraphic localisation of primary and metastatic NETs until very recently.[8]

The positron emitter gallium-68 (^{68}Ga) has gained great interest in nuclear medicine because of its suitable physical characteristics such as the high positron yield (89%), and the clinically useful half-life (68 min). This increased interest has triggered the development of many target-specific ^{68}Ga-based clinical trials.[9 10]

Targeting SSTR with ^{68}Ga has been particularly pursued for proof-of-principle clinical studies using positron emission tomography (PET).[11] In 2016, (gallium-68-DOTA0-Tyr3)-octreotate (^{68}Ga-DOTATATE (NETSPOT)) was approved by the Food and Drug Administration (FDA) in the USA.[12] Other promising SSTR PET radiopharmaceuticals, such as (gallium-68-DOTA0-Tyr3)-octreotide (^{68}Ga-DOTATOC) and (gallium-68-DOTA0-1NaI3)-octreotide (^{68}Ga-DOTANOC) are currently used for NET imaging[13 14] and have become the new standard for SSTR imaging using PET instead of ^{111}In-pentetreotide.[15]

Effectively, the DOTA peptide SSTR compounds have a similar diagnostic performance.[16–18]

There are at the moment a wide range of different automatic synthesis modules available, with variability in radiochemistry strategies, reagents and starting materials (figure 1) to produce these DOTA peptide SSTR compounds. Licensing these production methodologies with the regulatory authorities is therefore likely to be challenging.

The present phased study tested for the first time in humans diagnosed with grade 1 and 2 gastroenteropancreatic (GEP)-NET the safety and tolerability of a novel preformulated ^{68}Ga-DOTATOC kit with the eluate provided by commercially available germanium-68 (^{68}Ge)/^{68}Ga generators. Subsequently, we assessed the feasibility and robustness of implementing this new production methodology in a clinical service.

MATERIALS AND METHODS

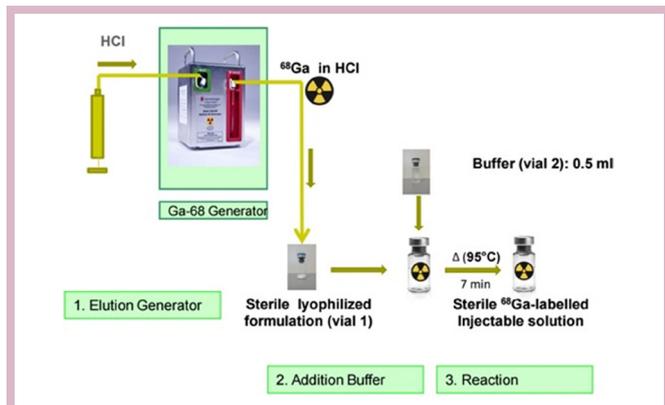### First in human investigational medicinal product (IMP) phase

A phase I–II clinical trial was carried out at two European Neuroendocrine Tumour Society (ENETS) Centres of Excellence (The Christie NHS Foundation Trust (Manchester, UK) and The Royal Free Hospital (London, UK). Written informed consent was obtained from each patient participating in the study.

Patients

Eligible patients were those who met all the following criteria: (1) patients with histologically confirmed GEP-NET; (2) grade 1 or 2 NET as per WHO 2010 classification,[3] confirmed by pathology central review; (3) previously assessed by CT/MRI within 3 months prior to enrolment; (4) age ≥18 years old; and (5) Eastern Cooperative Oncology Group (ECOG) Performance Status≤2.[19] Patients who were pregnant, had hypersensitivity to the investigational drug or any of its components or had significant ECG abnormalities at screening were excluded.
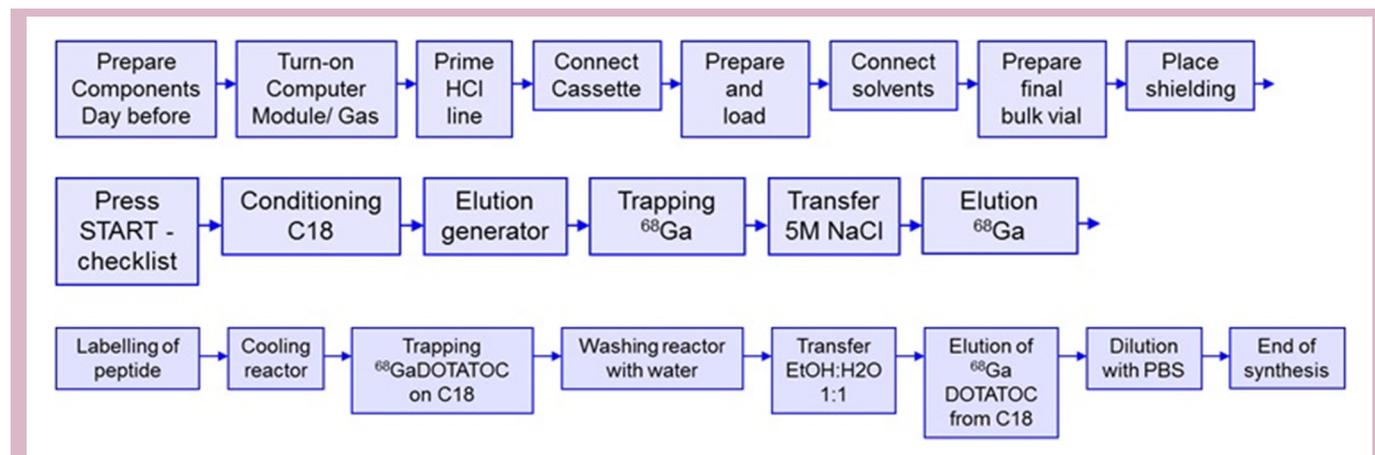
Figure 1 Radiolabelling scheme of ^{68}Ga-DOTA-peptides using an automatic synthesis module. HCl, hydrochloric acid; PBS, Phosphate-buffered saline.

Figure 2 Radiolabelling scheme for 68Ga DOTATOC (SomaKIT TOC).

Investigational medicinal product

The full name of the IMP was '68Ga-DOTA0-Tyr3-octreotide for intravenous injection SomaKIT TOC' (Advanced Accelerator Applications, New York, New York, USA), referred to as ^{68}Ga-DOTATOC for the purposes of this manuscript. The IMP was available as a 2-vial kit which consisted of a lyophilised formulation (vial 1) and a suitable buffer (vial 2) to be used in combination with a solution of ^{68}Ga in hydrochloric acid (HCl) as gallium chloride (^{68}GaCl$_3$) provided by a ^{68}Ge/^{68}Ga generator to obtain ^{68}Ga-DOTATOC as a radiolabelling imaging product for intravenous injection. Each monodose kit contained an amount of the active substance and excipients suitable for preparing up to 1110 MBq of injectable ^{68}Ga-DOTATOC. The kit was produced and supplied by the study sponsor (Advanced Accelerator Applications).

^{68}GaCl$_3$ eluate was obtained from a ^{68}Ge/^{68}Ga generator that had been eluted within the previous 24 hours. For the study, the Galliapharm ^{68}Ge/^{68}Ga generator (Eckert & Ziegler, Berlin, Germany) was used. In particular, and in accordance with the specifications indicated in the monograph, the potential release of the parent nuclide (^{68}Ge) must be guaranteed to be lower than 0.001% during the declared life of the generator. The eluate from the generator used was sampled and checked for ^{68}Ge breakthrough, iron and zinc content, bacterial endotoxins and tested for sterility every week in order to meet with the specifications indicated in the European Pharmacopoeia Monograph 'Gallium (^{68}Ga) chloride solution for radiolabelling'.[20 21] This postproduction assessment was performed partly by the study sites and the sponsor as per the requirement of the regularity authorities.

Each kit used for the study was prepared, packaged and released according to study protocols, local Standard Operating Procedures, Good Manufacturing Practice guidelines, International Council for Harmonisation and Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

^{68}Ga-DOTATOC was prepared on the day of the administration using as the reaction vial containing a lyophilised formulation of 40 µg of DOTATOC (vial 1) to be radiolabelled with ^{68}GaCl$_3$ (5 mL HCl 0.1 N solution—maximum activity 1110 MBq). Immediately after the elution, 0.5 mL of reaction buffer (vial 2) was added to vial 1. Vial 1 was then placed in a preheated dry bath (Labnet Accublock digital dry bath). After at least 7 min (but no more than 10 min) at 95°C, the final labelled ^{68}Ga-DOTATOC product was ready for the formal release after quality control (QC) testing. Visual check, pH, radiochemical purity (ITLC and radio-HPLC) and radionuclidic purity tests were performed in all the batches before release (figure 2). Mean finger doses of staff members working with the IMP production was 0.18 mSv (left) and 0.31 mSv (right) per production including quality control. This was similar to the synthesis modules. Axial body dosimetry measurements were also within safety thresholds.

Dose and mode of administration

Each patient was allocated a single treatment kit. The dose of ^{68}Ga-DOTATOC administered to each patient was calculated as 2 MBq/kg±10%, but not less than 100 MBq and not more than 200 MBq. The weight of the patient, amount of dose injected and the estimated time of injection were recorded. The dose was measured using a radionuclide dose calibrator (Capintec CR-15). ^{68}Ga-DOTATOC was administered intravenously by qualified staff.

For patients receiving treatment with long-acting SSAs somatostatin analogues), ^{68}Ga-DOTATOC administration was performed at least 4 weeks after the last administration of SSA. Treatment with short-acting SSAs was interrupted for 24 hours before the administration of ^{68}Ga-DOTATOC.

Whole-body PET-CT imaging acquisition

All patients underwent a whole-body PET-CT, at 40–60 min after administration as per the recommended guidelines.[13] Patients voided their urinary bladders immediately before imaging.

The patients were placed on the scanner table (either GE Discovery STE or Siemens Biograph mCT) to allow a vertex to mid-thigh low-dose CT scan without contrast (used for anatomic localisation and attenuation correction), followed immediately by emission imaging. Emission imaging was performed from vertex to mid-thigh, with 2–4 min per bed position (the range of bed position emission imaging took into account the different imaging equipment at the clinical trial sites) in 3-D acquisition mode.

Emission images were reconstructed using the proprietary VuePoint HD implementation of the 3-D ordered-subset expectation maximisation algorithm with two iteration of 28 subsets and a postreconstruction Gaussian filter of 6 mm.

Final images were stored using a 128×128 matrices set covering a 70 cm field of view at 3.27 mm slice separation. Emission data were corrected for dead time, scatter and decay, and resulting voxels were stored in units of Bq/ml. As per standard practice, all images were normalised
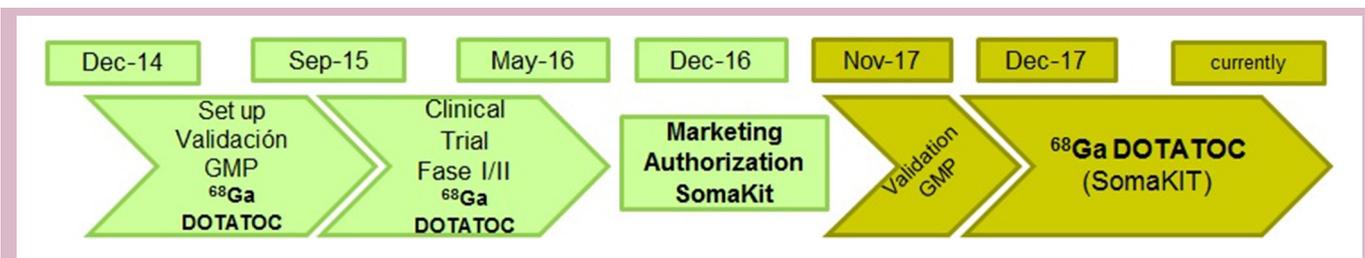
Figure 3 Schematic diagram of the study phases.GMP, Good Manufacturing Practice.

to the injected dose and patient weight to be expressed in the standardised uptake value. Attenuation correction was performed with CT using 120 kVp, with smart mAs (range, 30–440, with a noise index of 40) to ensure consistent image quality. Corresponding CT images were reconstructed into a 512 matrices covering 50 cm for anatomical information and also extended to 70 cm for attenuation correction

Diagnostic report

All study cases were reported as per standard of care by expert nuclear medicine physicians or oncology radiologists/nuclear medicine physicians (dually accredited).

Safety assessment and follow-up

Adverse events (AEs) were assessed using the Common Terminology Criteria for Adverse Event Classification version 4.03. The assignment of the causality for every AE was made by the investigator responsible for the care

of the participant (clinicians with expertise in the filed were delegated for this task as per GCP). Haematology, biochemistry and urinalysis were monitored before and after ^{68}Ga-DOTATOC injection (at baseline/screening visit, day 0 visit, day 7 visit and day 28 visit). Any AEs post injection were recorded and followed until resolution. Physical examination was performed prior to the injection and an ECG (12-lead) was recorded immediately after the administration. Vital signs were assessed before and at the end of the PET-CT examination.

After administration of the study product, two safety follow-up visits were performed at day 7 (±2 days) and day 28 (±3 days). All concomitant medications received from 2 weeks prior to the first administration date through the end of study were recorded at all study visits, including NET-related treatments.

The safety assessments were performed in all enrolled patients after a single administration of ^{68}Ga-DOTATOC.

Table 1 Adverse events and relationship to study drug administration

Adverse events	Possible N (%)	Probable N (%)	Unlikely N (%)	Unrelated N (%)
Headache	1 (4 %)			1 (4 %)
Nausea	1 (4 %)			1 (4 %)
Dysgeusia		1 (4 %)		
Paraesthesia		1 (4 %)		
Flushing			1 (4 %)	1 (4 %)
Lethargy			1 (4 %)	
Oropharyngeal pain			1 (4 %)	
Rhinorrhoea			1 (4 %)	
Vomiting			1 (4 %)	
Abdominal pain			2 (7 %)	1 (4 %)
Diarrhoea			2 (7 %)	2 (7 %)
Abdominal discomfort				1 (4 %)
Eye irritation				1 (4 %)
Influenza-like illness				1 (4 %)
Pancreatic insufficiency				1 (4 %)
Proctalgia				1 (4 %)
Upper respiratory tract infection				1 (4 %)
Back pain				2 (7 %)
Total	**2 (7 %)**	**2 (7 %)**	**9 (33 %)**	**14 (25 %)**

Table 2 Radiolabelling results for ^{68}Ga-DOTATOC

| Batch | Radiochemical purity—ITLC | | | pH | Activity (MBq) |
	Free ^{68}Ga (%)	^{68}Ga colloids (%)	^{68}Ga DOTATOC (%)		
1	0.38	0.19	99.43	3.5	748
2	0.90	1.23	97.87	3.6	714
3	0.82	0.33	98.85	3.5	710
4	0.08	0.18	99.74	3.5	652
5	0.39	0.59	99.02	3.6	545
6	0.20	0.55	99.25	3.5	419
7	0.32	0.39	99.29	3.5	408
8	1.70	0.28	98.02	3.5	473
9	0.08	0.22	99.70	3.6	544
10	0.37	0.59	99.04	3.5	526
11	0.66	0.40	98.94	3.8	506
12	0.80	0.25	98.95	3.5	496
13	1.41	0.21	98.38	3.5	696
14	0.72	1.28	98.00	3.2	575
15	1.07	0.40	98.53	3.2	470
16	0.79	0.01	99.20	3.2	494
17	0.41	0.15	99.44	3.2	488
18	1.14	0.33	98.53	3.2	895
19	1.16	0.72	98.12	3.2	840
20	0.90	1.02	98.08	3.2	701
Average	0.72	0.47	98.82	3.4	
Max	1.70	1.28	99.74	3.8	
Min	0.08	0.01	97.87	3.2	
SD	0.43	0.34	0.58	0.2	

ITLC, Instant Thin-Layer Chromatography.

Safety and tolerability were primarily evaluated by the incidence of ^{68}Ga-DOTATOC-related AEs, clinical laboratory values (haematology, biochemistry and urinalysis), vital signs (blood pressure and heart rate (HR)), ECG and physical examination findings. For analysis purposes, baseline for a given assessment was defined as the last non-missing value prior to the administration of ^{68}Ga-DOTATOC.

Implementing ^{68}Ga-DOTATOC SomaKIT TOC in a NET clinical service phase

One of the ENETS (The Christie NHS Foundation Trust) site then assessed the feasibility and robustness of this production methodology over a period of 11 months.

Using this new synthesis methodology post EMA licensing, 113 vials of ^{68}Ga-DOTATOC SomaKIT TOC were synthesised at The Christie NHS Foundation Trust between 21 November 2017 to 9 November 2018. Quality assurance and control parameters were identical to the first in human IMP phase. Figure 3 depicts the phases of the study.

Statistical methods
Sample size calculation

The target sample size considered sufficient to provide data to assess the safety and tolerability of ^{68}Ga-DOTATOC using this new methodology of synthesis was 20 evaluable patients (ie, patients who had completed the imaging protocol).

Analyses

Summary statistics were provided for demographic and baseline characteristics (sex age, weight, height, body mass index (BMI), NET type, grade and TNM stage). Descriptive statistics for continuous variables included the number of non-missing values, mean, SD and range. For categorical variables, descriptive statistics included counts and percentages per category.

Safety variables were tabulated at each measuring time and for change from baseline together with descriptive statistics, if appropriate.

For the clinical implementation phase, descriptive summary statistics of the number of vials that passed quality assurance check are reported.
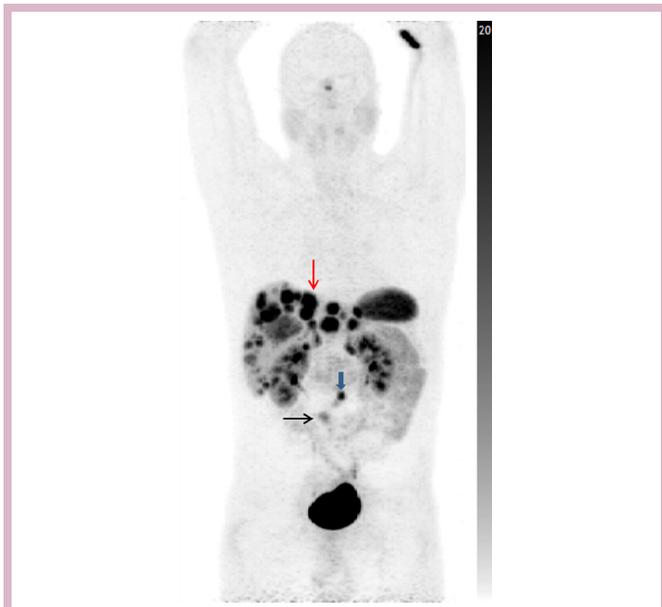
Figure 4 Patient example (coronal maximum intensity projection) demonstrating intense uptake within multiple liver metastases (red arrow), small bowel primary (horizontal black arrow) and focal midline uptake within nodal metastases (blue arrow).

RESULTS

First in human IMP phase

Twenty patients were screened and enrolled between June 2015 and June 2016. All twenty enrolled patients completed the study. There were no screen failures.

Baseline characteristics

Most of the patients were male (14 males; 6 females), and Caucasian (90%) with a mean (SD) age of 58 (12) years and mean (SD) BMI of 26 (4.5) kg/m². The mean (SD) time between first diagnosis of NET and enrolment in the study was 2.7 (3.3) years. Most patients had grade 1 NET (14 patients; 70%); 5 patients (25%) had grade 2; 1 patient not known. Fifteen (75%) had stage IV disease (stage I in one patient (5%), stage II in one patient (5%) and stage III in the remaining three patients (15%)). ECOG Performance Status was 0 and 1 in 15 (75%) of patients and 5 (25%) of the patients, respectively.

Fourteen (70%) patients had a primary tumour arising from the midgut. Three (15%), two (10%) and one (5%) patients had primary tumours arising from the foregut, pancreas and unknown primary (suspected gastrointestinal tract), respectively.

The most frequent prior and concomitant medications included: proton pump inhibitors (11 patients; 55%), SSA (9 patients; 45%) and pancreatic enzyme replacement preparations (7 patients; 35%).

Safety analysis

Twelve (60%) patients experienced at least one AE during the study. All the 27 AEs were classified as grade 1 (85%) or grade 2 (15%) severity. None of these AEs were considered by the investigators as serious or led to discontinuation of study procedures. No grade 3–4 AEs were identified.

The most commonly reported AEs were gastrointestinal disorders (n=14; 52%). Only two AEs were classified as 'possibly related' to the study drug administration (headache and nausea). In addition, another two AEs were classified as 'probably related' (dysgeusia and paraesthesia). See table 1 for complete details. Two (7%) AEs were unresolved at the end of the trial (both classified as not related to study drug).

The haematology and blood biochemistry values at each visit were compared with baseline levels. Despite statistically significant decreases between day 0 (day of imaging) and baseline of some of these parameters (decrease of mean red blood cells, haematocrit, haemoglobin, mean corpuscular volume, albumin and protein), the biological values remained within the normal ranges and the fluctuations were judged as not clinically significant (online supplementary file 1). No changes were observed between day 7 visit and day 28 visit compared with baseline. No liver or kidney function dyscrasia were identified.

Comparison between baseline (screening) ECG and ECG performed following ^{68}Ga-DOTATOC injection showed a significant increase in mean QT (p=0.0433) and PR (p=0.0187) intervals. However, these changes were not found to be clinically significant. No changes in QTcF interval were identified (p=0.6215).

No statistically significant changes in vital signs compared with baseline were observed; one patient experienced a significant decrease in the HR between baseline (screening) and following ^{68}Ga-DOTATOC injection and day 28 visits which was deemed to be not clinically significant.

^{68}Ga-DOTATOC kit preparation and administration

The results of QC testing of the kits released for injection were in compliance with the European Pharmacopoeia Monograph 'Gallium (^{68}Ga) edotreotide injection' guidelines. The mean radiochemical purity due to ^{68}Ga-DOTATOC was 98.82% (SD=0.58%, max=99.74%, min=97.87%; table 2).

In total, 23 kits were prepared for the study. In spite of optimising the labelling technique, three of these kits were not released as they did not meet the product specification. The procedure for the preparation of the kit was thus optimised during the duration of the study.

The final volume and activity (up to 1110 MBq) of the radiolabelled product provided a sufficient amount of solution for QC testing and for the subsequent administration (table 2). The stability studies performed on the drug product performed by the sponsor (outside the scope of this study) had demonstrated that the 2-vial kit (lyophilised formulation and buffer) is stable for 1 year when stored below 2°C–8°C. Once radiolabelled, the final ^{68}Ga-DOTATOC solution is stable for 4 hours when stored below 25°C.

Figure 5 Comparison of techniques. RP, radiopharmaceutical; MA, Marketing authorisation
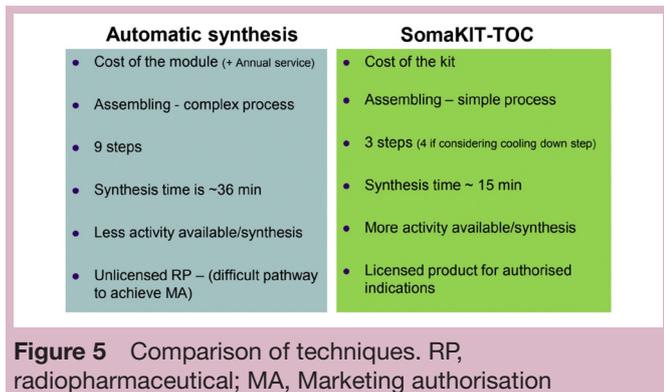
All the doses administered were in accordance with standard clinical practice for ^{68}Ga-DOTA peptides of 100–200 MBq, and following current European guidelines.[11] All patients received the radiopharmaceutical as per protocol except one patient who received a dose of 204 MBq and one patient who received a dose of 103 MBq (less than 2 MBq/kg±10%). Such deviations did not impact either safety or image quality.

Results from ^{68}Ga-DOTATOC PET imaging

The mean time of PET-CT scan was 58 min (SD=12) after the ^{68}Ga-DOTATOC injection, which was compliant with the protocol requirements.

All cases demonstrated normal physiological distribution of tracer as expected in ^{68}Ga-DOTATOC PET imaging with physiological uptake detected in the pituitary gland, adrenals, spleen, liver and uncinated process of the pancreas.

Two out of 20 (10%) PET scans were assessed as negative by the investigator which means that no tumour lesions were observed; both of these patients had undergone curative surgery and negative scans were anticipated. A maximum intensity projection image of a patient with metastatic disease involving both lobes of the liver, mesenteric nodal disease and a small bowel primary in situ with physiological distribution is illustrated as an example (figure 4).

Implementing ^{68}Ga-DOTATOC SomaKIT TOC in a NET clinical service phase

Results

Of the 113 vials of ^{68}Ga-DOTATOC SomaKIT TOC synthesised, only 2/113 were rejected due to detection of higher than permitted ^{68}Ga impurities (online supplementary file 2). After further investigation, the reason for the two vials containing higher than permitted ^{68}Ga impurities

	n	Number of failures	Failure rate
Synthesis module	246	8	3.25%
SomaKIT-TOC	113	2	1.77%

Figure 6 Comparison between production by synthesis module and SomaKIT TOC.

was due to contact of the elute with components of the primary package (stopper). Production methodology was further optimised to make sure that the contents of the kit is not shaken or inverted during the labelling process.

The synthesised tracer was then safely used to image patients with grade 1/2 in the NET clinical service.

DISCUSSION AND CONCLUSION

This phased study has demonstrated the safety and tolerability of a new 'ready-to-use' kit for preparation of ^{68}Ga-DOTATOC for injection in patients with GEP-NETs. The new synthesis methodology was also successfully implemented in the clinical service for NET imaging with a satisfactory toxicity profile.

The advent of SSTR scintigraphy has revolutionised the understanding of the pathophysiology of NETs and staging of this disease. The development of this targeted tumour tracer imaging technique was further advanced with numerous SSTR PET radiopharmaceuticals that have been proven to be more sensitive, specific and more importantly has led to a change in the clinical decision-making process when compared with the SSTR scintigraphic technique.[22–24] In the last decade, several clinical studies have compared the diagnostic role of different ^{68}Ga-DOTA-peptides (using PET-CT image acquisition) to ^{111}In-pentetreotide (OctreoScan) (using single photon emission CT (SPECT)/SPECT-CT image acquisition) in patients diagnosed with NETs; results favoured the use of these ^{68}Ga-DOTA-peptides in: (1) detecting small tumours or tumours bearing only a low density of SSTR, (2) offering excellent imaging properties and very high tumour/background ratios, (3) better intrinsic spatial resolution and (4) detecting additional lesions and altering clinical management.[25–30]

In addition to imaging with diagnostic purposes, SSAs labelled with beta emitters such as lutetium-177 (^{177}Lu) or yttrium-90 (^{90}Y) are used for targeted treatment (the so-called peptide receptor radionuclide therapy or PRRT[31]) of patients diagnosed with advanced NETs. Haug et al demonstrated that a decrease in ^{68}Ga-DOTATATE uptake in tumours after the first cycle of PRRT predicted improved time to progression and correlated with an improvement in clinical symptoms among patients with well-differentiated NETs.[32]

Interestingly, the above-mentioned peptides may be labelled with either diagnostic (γ and positron emitters (such ^{68}Ga)) or therapeutic (α and β emitters (such as ^{213}Bi/ ^{225}Ac and ^{177}Lu/^{90}Y)) radiopharmaceuticals, providing an integrated 'theranostic' management protocol for NETs.[33] Such a theranostic approach allows the identification of specific tumour biological targets, in order to select the optimal therapeutic radio-labelled ligands for individual patients.

The PET radiopharmaceuticals fit better into a theranostic pathway for patients with NET due to their superior sensitivity, specificity and imaging technology. However, for many years, unlicensed PET radiopharmaceuticals

have been produced with 'in-house' synthesis modules and techniques that were based on a multistep process. Multi-step processes that could and do lead to multiple points of failure and errors. Due to the different approaches to producing the final injectable PET SSTR radiopharmaceutical, the final product using these synthesis modules was difficult to or nearly impossible to be licensed by the pharmaceutical licensing agencies (FDA and EMA; figure 5).

There are some limitations worth mentioning regarding this study. First, the limited samples size was adequate to address the primary and secondary end-points and provide descriptive analysis; however, there was limited power for inferential statistics (ie, 95% CI). In addition, this study explored the safety profile of a single injection of the tracer; safety of repeat dose administration cannot be commented on.

Based on the results of this first-in-human study, the EMA approved the IMP kit in December 2016, which has led to the world's first licensed ^{68}Ga-DOTATOC radiopharmaceutical for the utility of PET imaging in patients with NETs. This product is now available as the licensed gallium-labelled DOTATOC NET PET radiopharmaceutical. In the light of these data, the analysis of our ^{68}Ga-DOTATOC study provide convincing results to further pursue the clinical use of the kit for the preparation of ^{68}Ga-DOTATOC for injection.

The kit used in our study circumvents the need for institutional production of imaging tracers with the inherent quality risks and represents the next revolution in the evolution of PET radiopharmaceuticals. This markedly simplified production methodology has been proven to be safe in our study. The production methodology was then successfully implemented into clinical practice. We demonstrated that this licensed product has a robust synthesis methodology and is similar with regards to synthesis of the final radiopharmaceutical product for patient utility when compared with unlicensed synthesis module (figure 6). This practice-changing development will allow a larger group of clinical team's patients' access to a licensed product without the need for a synthesis module.

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Contributors PM and JV in collaboration with AAA developed and conceived this trial. They also actively participated setting up and carrying out this clinical trial. AL, SN, JC, PSC, PJ, MS and MC actively participated in this trial, including setting up the trial, technical and procedural aspects of the trail. PM drafted the manuscript. All authors had the opportunity to further revise the manuscript and approved the final version.

Competing interests PM and JV declare Consulting/Advisory roles for AAA. PM, AL, JV and JC declare Speakers' Bureau for AAA. AL has received education and travel support from AAA. MS was AAA's Chief Medical Officer until September 2017 of and has continued her collaboration as Medical Advisor.

Patient consent for publication Not required.

Ethics approval The study (European Clinical Trials Database reference number 2014-002741) had Research Ethics Committee, Medicines & Healthcare products Regulatory Agency and Administration of Radioactive Substances Advisory Committee approvals. The study was performed in accordance with the principles of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study have been included in the manuscript.

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