CLINICAL STUDY REPORT

DOTATOC

VHIO18001

PATTERNS OF UPTAKE OF ^{18}F-FDG AND ^{68}GA-DOTA PET IN ADVANCED NEUROENDOCRINE TUMORS

Document type:	Clinical Study Report
Development phase:	IV
Protocol number:	VHIO18001
EudraCT number:	2018-000398-64
Sponsor	Vall d' Hebron Institute of Oncology (VHIO)

1 Study information

Study title: Patterns of uptake of ^{18}F-FDG and ^{68}Ga-DOTA PET in advanced neuroendocrine tumors

Test drug/Investigational product: SomaKit TOC (edotreotide or DOTATOC)

Indication studied: Diagnosis of neuroendocrine tumors

Study design: A prospective, unicentric phase IV study in patients with advanced neuroendocrine tumors (NETs).

Sponsor: Vall d'Hebron Institute of Oncology (VHIO)

Protocol identification: VHIO18001. Version 2.0; 22 May 2018

Statistical report identification: Version 3.0; 26 May 2020

Development phase of study: IV

Study initiation date: 07 November 2018 (first patient enrolled)

Study completion date: 04 June 2019

Principal or Coordinating Investigators:

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Company/Sponsor signatory:

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Statement: This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Report date(s): 15 June 2021

Earlier reports from the same study: 28 April 2021 (Draft 0.1)

2 Synopsis

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Edotreotide (DOTATOC)</td></tr>
<tr><td colspan="3">STUDY CODE:
VHIO18001</td></tr>
<tr><td colspan="3">TITLE OF STUDY:
Patterns of uptake of ^{18}F-FDG and ^{68}Ga-DOTA PET in advanced neuroendocrine tumors</td></tr>
<tr><td colspan="3">PRINCIPAL INVESTIGATOR:
Marc Simó, MD, Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain</td></tr>
<tr><td colspan="3">STUDY CENTRES:
Hospital Universitari Vall d'Hebron, Barcelona, Spain</td></tr>
<tr><td colspan="3">PUBLICATION (REFERENCE):
NA</td></tr>
<tr><td colspan="3">STUDY PERIOD (YEARS):
Date of first enrolment/first subject first visit: 07/NOV/2018
Date of last completed/last subject last visit: 04/JUN/2019</td></tr>
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Not applicable.</td></tr>
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The objectives were as follows:</td></tr>
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Name of Active Ingredient: Edotreotide (DOTATOC)		

- To determine the sensitivity of ^{68}Ga-DOTATOC PET/CT to detect tumors with high expression of RSST as compared to that of standard of care with octreotide labeled with gamma-emitting radionuclides in patients with neuroendocrine tumors (NETs).
- To identify the uptake patterns of ^{18}F-FDG and ^{68}Ga-DOTATOC PET/CT within subjects with well or moderately differentiated metastatic NET (ENETS grades 1 and 2).
- To establish the correlation between the functional characteristics of hepatic lesions and the level of uptake of ^{18}F-FDG and ^{68}Ga.
- To explore the impact of this combined imaging test on therapeutic management.

METHODOLOGY:

This was a prospective, unicentric phase IV study to assess whether the incorporation of ^{68}Ga-DOTATOC imaging modality increased the detection of tumor lesions in patients with G1 and G2 metastatic NETs.

A NET multidisciplinary committee determined if a patient met the requirements to participate in the study. During the selection visit, exclusion and inclusion criteria were applied; with recording of full medical history. All patients underwent a whole-body ^{68}Ga-DOTATOC PET/CT. The maximum time interval between the routine imaging scans (^{99}mTc-Tektrotyd SPECT and ^{18}F-FDG PET/CT) and ^{68}Ga-DOTATOC PET/CT should not exceed 30 days. After the ^{68}Ga-DOTATOC PET/CT scan was performed, a safety follow-up visit was scheduled at day 3.

In a second phase, we explored the therapeutic impact of the combined imaging on the patient's management.

NUMBER OF SUBJECTS (planned and analysed):

No. planned:	30
No. screened:	30
No. treated:	30
No. analyzed for efficacy:	30

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No. analyzed for safety:	30
No. completed the study:	30

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Patients eligible for inclusion in this study had to fulfil all of the following criteria:

1. Patients older than 18 years.
2. Grade 1 and 2 NETs according to WHO and ENETS classification.
3. Metastatic NETs.
4. Life expectancy > 12 months
5. Signed written informed consent.

Exclusion criteria:

1. Grade 3 NET according to WHO and ENETS classification.
2. Previous systemic radiopharmaceutical therapy.
3. Pregnancy patients.
4. Patients with high-risk disease (cardiovascular, pulmonary).
5. Patients with chronic liver disease.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

- **Name:** SomaKit TOC
- **Strength:** 40 mg
- **Pharmaceutical Form**: Kit for radiopharmaceutical preparation
- **Route of Administration**: Intravenous use
- **Content:** Powder for solution for injection: 40 mg; Reaction Buffer: 1 ml
- **MAH:** Advanced Accelerator Applications

Name of the Sponsor/Company: VHIO	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**
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Name of Active Ingredient: Edotreotide (DOTATOC)		

DURATION OF TREATMENT:

NA. SomaKit TOC (edotreotide, also known as DOTATOC) is only use for diagnosis of NETs.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

NA

CRITERIA FOR EVALUATION:

- Comparison of sensitivity of ^{68}Ga-DOTATOC PET/CT and ^{99}mTc-Tektrotyd SPECT/CT in metastatic NETs.
- Comparison of sensitivity of ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT in metastatic NETs.
- Impact of combined ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT imaging on therapeutic management in patients with NETs.

STATISTICAL METHODS:

Descriptive summary statistics for categorical/qualitative variables included frequency count (n) and percentage (%). Descriptive summary statistics for continuous/quantitative variables included arithmetic mean and standard deviation for normally distributed data, and median with data range (minimum to maximum, interquartile range or percentile range) for data not normally distributed.

Differences in the categorical variables were evaluated by the McNemar's test and the Wilcoxon signed rank test was used for quantiative variables. A P value < 0.05 was considered to indicate statistical significance.

SUMMARY AND CONCLUSION(S):

EFFICACY RESULTS:

The study included 30 patients. The median age for the whole study population was 58 years, with a range of 36-82 years, and 63% were male. Nearly half of patients had pancreatic cancer and 77% had G2 differentiation.

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There was no statistically significant difference between ^{68}Ga-DOTATOC PET/CT and ^{99}mTc-Tektrotyd SPECT in detection rate of primary tumor site (39% in both modalities). However, ^{68}Ga-DOTATOC PET/CT showed significantly higher detection rate for loco-regional metastatic lesions versus ^{99}mTc-Tektrotyd SPECT (63.3% vs 43.3% positive patients; p = 0.034). Although the positive rate for distant metastasis was similar to ^{99}mTc-Tektrotyd SPECT, ^{68}Ga-DOTATOC PET/CT showed a significantly higher number of identified distant lesions. Specifically, significant more tumor lesions per patient were found in liver (p=0.004), infra-nodal (p= 0.05) and supra-nodal regions (p=0.046).

There was no statistically significant difference between ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT imaging modalities in detection rate of primary tumor site (38% vs 31%; p>0.05). However, ^{68}Ga-DOTATOC PET/CT shows significantly higher detection rate for loco-regional tumor lesions and for global tumor lesions versus ^{18}F-FDG PET/CT (p <0.001). Sensitivity of ^{68}Ga-DOTATOC PET/CT for detection of regional lymph node metastasis was 63.3% vs 20% with ^{18}F-FDG PET. ^{68}Ga-DOTATOC PET/CT showed a detection rate of 100% of distant metastasis compared to 67% with ^{18}F-FDG PET/CT (p<0.05). Based on the location of lesions, there were no significant differences between either imaging procedure in the number of lesions identified in any of the regions.

Therapeutic management was changed in 67% of patients after the additional data provided by ^{68}Ga-DOTATOC PET/CT imaging.

SAFETY RESULTS:

^{68}Ga-DOTATOC PET/CT imaging test was well tolerated by all the participants, and no immediate or delayed adverse event was reported by the subjects during the two-day follow-up after the probe injection.

CONCLUSIONS:

In conclusion, compared to routine ^{99}mTc-Tektrotyd SPECT and ^{18}F-FDG PET/CT imaging, ^{68}Ga-DOTATOC PET/CT appeared to have a greater sensitivity in the detection of the presence of loco-regional and distant metastases in patients with G1/G2 advanced NETs. Moreover, ^{68}Ga-DOTATOC PET/CT compared to ^{99}mTc-Tektrotyd SPECT has de potential to detect more lesions in the liver, infra-nodal and

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supra-nodal regions. ^{68}Ga-DOTATOC PET/CT, ^{18}F-FDG PET/CT and ^{99}mTc-Tektrotyd SPECT have a comparable diagnostic value in the detection of primary lesions of NETs. Therapeutic management of most patients changed after ^{68}Ga-DOTATOC PET/CT, underling the importance of ^{68}Ga-DOTATOC PET/CT incorporation into the clinical routine of NET patients. Prospective studies with a larger patient group would be beneficial in the future.

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4 List of abbreviations and definition of terms

^{68}Ga-DOTATOC	^{68}Ga-edotreotide
AE	Adverse event
AEMPS	Spanish Medicines and Health Products Agency
CRA	Clinical Research Associate
CRO	External or contract clinical research organization
CT	Computed tomography
DOTATOC	Edotreotide
EMA	European Medicines Agency
e-CRF	Electronic case report form
ENETS	European Neuroendocrine Tumor Society
FDA	Food and Drug Administration
FDG	^{18}F-fludeoxyglucose
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
MAH	Marketing Authorization Holder
MRI	Magnetic resonance imaging
NET	Neuroendocrine tumor
PET	Positron emission tomography
PET/CT	Positron emission tomography/computed tomography
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
SPECT	Single photon emission computed tomography

SPECT/CT	Single photon emission computed tomography/ computed tomography
SST	Somatostatin
SSTR	Somatostatin membrane receptor
SSTR2	Somatostatin receptor subtype 2
SUV	Standardized uptake value
WHO	World Health Organization

5 Ethics

5.1 Independent ethics committee or institutional review board

The study protocol was reviewed and approved by the Ethics Committee for research with medicinal products (CEIm) of Hospital Vall d'Hebron.

5.2 Ethical conduct of the study

The study was conducted according to the ethical principles of the Declaration of Helsinki.

5.3 Patient information and consent

Informed consent was obtained from each patient in writing at screening, before collecting any study-related data. All subjects received written and verbal information regarding the study. The given information emphasized that participation in the study was voluntary and that the subject could withdraw from the study at any time and for any reason. All subjects were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study.

6 Investigators and study administrative structure

The Principal Investigator for the study was Marc Simó, MD. This was a unicentric study conducted in the Vall d'Hebron University Hospital, Barcelona.

7 Introduction

Neuroendocrine tumors (NETs) constitute a heterogeneous group of neoplasms that originate from the endocrine system of the gastrointestinal tract or pancreas (Hauso et al. 2008). Neuroendocrine tumors are considered rare tumors with an estimated incidence of 1-5 cases per 100,000 person-years (van der Zwan et al. 2013).

The 2010 European Neuroendocrine Tumor Society (ENETS)/World Health Organization (WHO) classify NETs based on the mitotic index and Ki67-cell proliferation markers into low-grade (G1), moderate-grade (G2) and high-grade (G3) ('WHO Classification of Tumours of the Digestive System' 2011). Neuroendocrine tumors demonstrate a variable clinical behavior depending on the primary location and the differentiation of the tumor. Poorly differentiated carcinomas are characterized by aggressive behavior and poor survival (Cives and Strosberg 2018). These neoplasms can also be divided into functioning tumors, secreting a variety of peptide hormones, and non-functioning forms often metastatic at diagnosis.

The diagnosis and staging of NETs include a multidisciplinary approach combining morphologic and functional imaging modalities. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) provide detailed, anatomic information on the primary-tumor location and identify regional and distant metastases. However, their results are limited because of the small sizes, variable anatomic locations of NETs, and low metabolic rates (Shi et al. 1998). Functional imaging modalities with single photon emission computed tomography (SPECT)/CT or positron emission tomography (PET)/CT using adequate radiotracers allow for accurate delineation of disease extent and can also identify an occult primary tumor. Additionally, functional imaging allows for noninvasive characterization of tumoral functional status and heterogeneity based on analysis of the uptake intensity of target-specific tracers (Baumann et al. 2016).

Most NETs express a moderate-to-high density of somatostatin membrane receptors (SSTRs) that have been the target for molecular imaging techniques. Synthetic somatostatin analogs, such as octreotide, have been radiolabeled with γ-emitters (^{111}In, ^{123}I, or ^{99}mTc). Although octreotide scan with SPECT has been considered as the gold standard for the detection of NETs, the technique was limited by low image quality, limited spatial resolution and prolonged imaging protocol (Maxwell et al. 2014; Kaltsas, Besser, and Grossman 2004; Barrio et al. 2017). A novel class of somatostatin analogs labeled with the positron-emitting radionuclide ^{68}Ga (gallium) for PET imaging has emerged to overcome the deficiencies and disadvantages of octeodrite SPECT scans. There are several ^{68}Ga-labeled tracers that are in clinical use (^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC) (Deroose et al. 2016). All ^{68}Ga-DOTA-peptides show high affinity for SSTR2, the most overexpressed SSTR subtype. Smaller lesions as well as lesions with low-to-moderate SSTR expression can also be better detected using ^{68}Ga-DOTA-peptide PET imaging versus ^{111}In-DTPA-octreotide SPECT (Buchmann et al. 2007; Gabriel et al. 2007; Deppen et al. 2016; Krausz et al. 2011). Moreover, PET have some advantages over SPECT imaging, such as a higher sensitivity and its spatial resolution (Kumar et al. 2014; Rahmim and Zaidi 2008). Several papers have reported the diagnostic accuracy of ^{68}Ga-SSTR PET/CT for the characterization of NETs, evaluating a wide range of sensitivities and specificities (Ambrosini et al. 2012; Treglia et al. 2012; Yang et al. 2014; Geijer and Breimer 2013; Mojtahedi et al. 2014). Studies comparing diagnostic efficacy reported a superior performance of ^{68}Ga-DOTA PET/CT compared to SSTRs scintigraphy and other PET radiopharmaceuticals (Buchmann et al. 2007; Sadowski et al. 2016; Morgat et al. 2016; Srirajaskanthan et al. 2010; Van Binnebeek et al. 2016).

Neuroendocrine tumors lesions have different metabolic behavior depending on their histological characteristics and different expression of SSTRs according to the degree of differentiation. Low-grade NTs are usually moderately or well differentiated and, hence, express SSTRs on their cell

membrane. High-grade NTs, originate from poorly differentiated cells, commonly have low or absent SSTR expression and tend to have higher glycolytic and metabolic rates (Tirosh and Kebebew 2018). Thus, PET/CT with ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET/CT) is indicated in high grade and poorly differentiated forms of NET as reflects increased cancer cell glucose metabolism (Sharma et al. 2014; Chen et al. 2018). However, neuroendocrine tumors can present a high-level intra-lesion heterogeneity making the therapeutic choice difficult (Dagogo-Jack and Shaw 2018). Consequently, it is suggested that combining both ^{18}F-FDG PET/CT and ^{68}Ga-DOTA PET/CT for the management of neuroendocrine tumors particularly G2 and G3 may allow a more accurate identification of tumor lesion types; thus, guiding clinicians to the proper treatment options.

We conducted a prospective study to assess whether the incorporation of ^{68}Ga-DOTA imaging modality increased the detection of tumor lesions in patients with G1 and G2 metastatic NETs. We also studied whether the combined imaging (^{18}F-FDG and ^{68}Da-DOTATOC PET/CET) influenced the therapeutic strategy.

8 Study objectives

8.1 Primary objectives

- To determine the sensitivity of ^{68}Ga-DOTATOC PET/CT to detect tumors with high expression of RSST as compared to that of standard of care with octreotide labeled with gamma-emitting radionuclides.
- To identify the uptake patterns of ^{18}F-FDG and ^{68}Ga-DOTATOC PET/CT within subjects with well or moderately differentiated metastatic NETs (ENETS grades 1 and 2).
- To establish the correlation between the functional characteristics of hepatic lesions and the level of uptake of ^{18}F-FDG and ^{68}Ga.
- To explore the impact of this combined imaging test on therapeutic management.

8.2 Secondary objectives

There were no secondary objectives.

8.3 Exploratory objectives

Not applicable.

9 Investigational plan

9.1 Study design

This was a prospective, unicentric phase IV study to assess whether the incorporation of ^{68}Ga-DOTATOC PET/CT imaging modality increased the detection of tumor lesions in patients with G1 and G2 metastatic NETs.

A NET multidisciplinary committee determined if a patient met the requirements to participate in the study. During the selection visit, exclusion and inclusion criteria were applied; with recording of full medical history. All patients underwent a whole-body ^{68}Ga-DOTATOC PET/CT. The maximum time interval between the routine imaging scans (^{99}mTc-Tektrotyd SPECT and ^{18}F-FDG PET/CT) and ^{68}Ga-DOTATOC PET/CT should not exceed 30 days. After the ^{68}Ga-DOTATOC PET/CT scan was performed, a safety follow-up visit was scheduled at day 3.

In a second phase, we explored the therapeutic impact of the combined imaging on the patient's management.

The procedures and measurements assessed are detailed for each visit in **¡Error! La autoreferencia al marcador no es válida.**

Table 1. Schedule of Assessments

	Day -30 to 0	Day 1	End of study (day 3)
Eligibility criteria	×		
Informed consent[1]	×		
Demographic data			
Medical history			
Routine Imaging Tests[2]	×		
68Ga-DOTATOC PET/CT		×	
Adverse events		×	× (phone contact)

[1] Patients were previously assessed by a NET Multidisciplinary Committee.

[2] All the participating patients had already undergone a routine imaging test which included ^{99}mTc-Tektrotyd SPECT and ^{18}F-FDG PET/CT before inclusion in this study, as per routine clinical practice.

9.2 Population

9.2.1 Inclusion criteria

1. Patients older than 18 years.
2. Grade 1 and 2 NETs according to WHO and ENETS classification.
3. Metastatic NETs.
4. Life expectancy > 12 months.
5. Signed written informed consent.

9.2.2 Exclusion criteria

1. Grade 3 NET according to WHO and ENETS classification.
2. Previous systemic radiopharmaceutical therapy.
3. Pregnancy patients.
4. Patients with high-risk disease (cardiovascular, pulmonary).
5. Patients with chronic liver disease.

9.3 Treatment

9.3.1 Treatment administered

SomaKit TOC is a radiopharmaceutical composed of edotreotide, a somatostatin analogue. It is a kit for radiopharmaceutical preparation to be radiolabeled with gallium (^{68}Ga) chloride obtained from a germanium (^{68}Ge)/gallium (^{68}Ga) generator. The solution obtained, known as gallium (^{68}Ga) edotreotide (^{68}Ga-DOTATOC), is intended for the diagnostic work-up of NETs by PET. ^{68}Ga-edotreotide binds to SSTR. Tumors which do not bear SSTR will not be visualized.

9.3.2 Identity of the investigational product

Name	SomaKit TOC
Strength	40 mg
Pharmaceutical Form	Kit for radiopharmaceutical preparation
Route of administration	Intravenous use
Packaging*	Powder: vial (glass); Reaction Buffer: vial (COP)
Content	Powder for solution for injection: 40 mg; Reaction Buffer: 1 ml
MAH	Advanced Accelerator Applications

*Each pack contains:

- One vial of powder for solution for injection: 10 ml Type I glass vial closed with a chlorobutyl rubber stopper and sealed with a flip-off cap. Each vial contains 40 mg of edotreotide.

- One vial of buffer: 10 ml cyclic olefin polymer vial closed with a teflon stopper and sealed with a flip-off cap. Each vial contains 1 ml of reaction buffer.

The gallium (^{68}Ga) edotreotide solution for intravenous injection was prepared according to aseptic procedure, local regulation and the instructions specified in the summary of product characteristics (SmPC).

9.3.3 Method of assigning patients to treatment groups

There was one treatment group in this study and, therefore, no randomization of treatment assignment was necessary. Before enrolling a patient, the Investigator and the NET committee assured that the patient was eligible according to the Inclusion and Exclusion Criteria listed in Sections 9.3.1 and 9.3.2.

9.3.4 Selection of dose(s) in the study

The dosimetry of gallium (^{68}Ga) edotreotide was calculated by Sandstrom et al. (2013), using OLINDA/EXM 1.1 software. The effective dose resulting from the administration of an activity of 200 MBq to an adult weighing 70 kg is about 4.2 mSv.

For an administered activity of 200 MBq the typical radiation dose to the critical organs, which are the urinary bladder wall, the spleen, the kidneys and the adrenals, are about 24, 22, 16 and 15 mGy, respectively.

See the SmPC of Somakit TOC for more details.

9.3.5 Blinding

This was a single-arm, open label study that was not blinded.

9.3.6 Prior and concomitant therapy

Throughout the study investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. In case of Concomitant use of somatostatin analogues, it was preferable to perform imaging with gallium (^{68}Ga) edotreotide the day(s) before the next administration of a somatostatin analogue.

9.3.7 Treatment compliance

Patients underwent ^{68}Ga-DOTATOC PET/CT at the study site; therefore, treatment compliance was assessed by monitor's review of the dose administration CRF.

9.4 Efficacy, safety and other assessments

9.4.1 Efficacy assessments

- Comparison of sensitivity of ^{68}Ga-DOTATOC PET/CT and ^{99}mTc-Tektrotyd SPECT in metastatic NETs.
- Comparison of sensitivity of ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT in metastatic NETs.
- Impact of combined ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT imaging on therapeutic management in patients with NETs.

There were no secondary endpoints.

9.4.2 Safety assessments

All patients were followed for safety two days after the ^{68}Ga-DOTATOC PET/CT scan was performed. Full information about the definition of adverse events (AEs) and serious adverse events (SAEs), the procedures for reporting them and the assessment of other safety variables was given in the study protocol.

All reported AEs were coded using MedDRA (version 22.1). SAEs and AEs were tabulated by treatment group using standard coding terms sorted by System Organ Class (SOC) and Preferred Term (PT). The incidence of AEs in each treatment arm was tabulated by seriousness, severity, and relationship to study drug.

9.4.3 Appropriateness of assessments

The study assessments selected are standard for this indication/patient population.

9.4.4 Drug Concentration Measurements

Not applicable.

9.5 Data quality assurance

9.5.1 Monitoring

The investigator was required to maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on electronic case report forms (eCRFs) was required to be traceable to these source documents in the patient's file. The

investigator was also required to keep the original informed consent forms signed by the patient (a signed copy was given to the patient).

The investigator provided the monitor access to all relevant source documents to confirm their consistency with the e-CRF entries, when required. Sponsor monitoring standards required full verification for the presence of informed consents, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that was used for all primary and safety variables. Additional checks of the consistency of the source data with the e-CRFs have been performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.5.2 Data collection

An on-line e-CRF was created. The investigators recorded all the data on it directly via a web page.

Source documents were those that provide evidence of the patient's existence and ensure the integrity of the data collected in the e-CRF.

All the data on the patient's participation in the study and clinical condition during the study period was recorded / filed in the patient's medical record. These data are defined as source data. Medical information relevant for the assessment of efficacy and safety have been transcribed in the e-CRF specifically designed for the study and previously recorded in the medical record.

During the monitoring visits, the consistency between the patient's medical records and the data in the e-CRF was checked. e-CRF data from source documents had to be consistent with these; any discrepancy had to be justified.

A file was kept in each participating center with the study documentation, essential documents, including the protocol, information on the electronic case report forms, original signed informed consent forms, notifications of SAEs and authorizations from the IECs, health authorities, and other documentation required to ensure compliance with good clinical practices.

9.5.3 Database management and quality control

The data required for the analysis have been recorded by the investigators and sent electronically to a central database by an e-CRF. The system works on the Internet, with a real-time data recording system (on-line). The e-CRF data are not recorded in the investigator's local computer.

During the study, the monitor was responsible for ensuring that the study is being conducted in compliance with good clinical practice and current legislation, verifying, among other procedures, that

written informed consent has been obtained correctly from all patients, that the study procedures have been followed as shown in this protocol, and that the data have been precisely and reliably recorded, for which the information available in the medical records (source documents) was compared with the data recorded in the e-CRFs.

9.6 Statistical methods

9.6.1 Data analysis

Descriptive summary statistics for categorical/qualitative variables included frequency count (n) and percentage (%). Descriptive summary statistics for continuous/quantitative variables included arithmetic mean and standard deviation for normally distributed data, and median with data range (minimum to maximum, interquartile range or percentile range) for data not normally distributed.

Differences in the categorical variables were evaluated by the McNemar's test and the Wilcoxon signed rank test was used for quantiative varibles. A P value < 0.05 was considered to indicate statistical significance. Analyses have been performed using Stata version 15.1 (StataCorp, USA).

9.6.2 Determination of Sample Size

The sample size was determined by the possibilities of inclusion of patients in the study center during one year. However, the comparative series previously published between metabolic tracers such as ^{68}GaDOTATOC/NOC/TATE vs ^{18}FDG or ^{111}In-octreotide vs ^{99}mTc-Tektrotyde have been performed on a similar number of patients (N=20-40). In these series, the differences between the evaluated tracers were sufficient to provide statistical significance (Gabriel et al. 2003).

9.7 Changes in the conduct of the study or planned analyses

There were no relevant amendments to this protocol.

A Statistical Analysis Plan (SAP) was produced prior to statistical analysis as detailed in the protocol and the statistical analyses were carried out as indicated in the SAP.

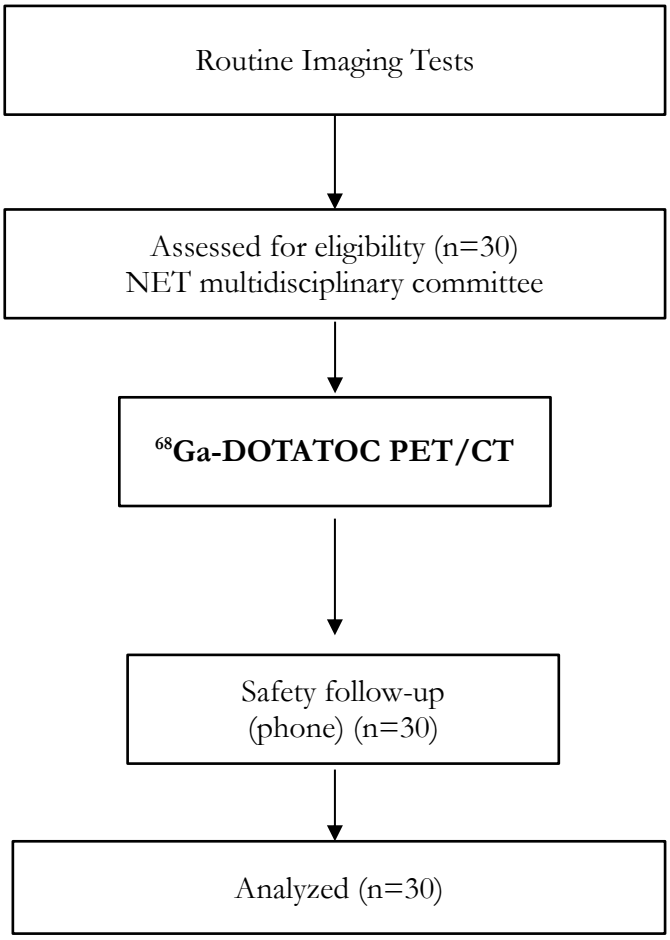
10 Study patients

10.1 Disposition of patients

Thirty patients were included in this study. All patients underwent ^{68}Ga -DOTATOC PET/CT and were followed-up for safety until two days after the imaging probe.

Figure 1 shows the flow of patients through the study.

Figure 1. Study flow-chart



10.2 Protocol deviations

One protocol deviation was identified related to inclusion/exclusion criteria. Patient #19 had Grade 3 NET according to WHO and ENETS classification (Ki67 35%). However, it was judged that this deviation would not cause any problems in evaluation of efficacy and safety of study product.

11 Efficacy evaluation

11.1 Data sets analyzed

All analyses were performed with all patients participating in the study.

11.2 Demographic and other patient characteristics

A summary of patient characteristics is presented in Table 2. The median age for the whole study population was 58 years, with a range of 36-82 years, and 63.3% were male. According to the WHO classification, 7 patients (23%) had G1 tumor differentiation and 23 patients (77%) had G2

differentiation. Nearly one half of patients had pancreatic cancer, and the other half had extra-pancreatic tumor.

Table 2. Demographic and Basic Clinical Characteristics (n=30)

Characteristic	n	%
Age (years)		
Median	58.1	
Range	36-82	
Gender		
Male	19	63.3
Female	11	36.7
Tumor differentiation grade		
G1	7	23.3
G2*	23	76.7
Tumor location		
Pancreatic	14	46.7
Extra-pancreatic	16	53.3
Temporary stoma		
No	4	17.4
Yes	19	82.6
Functional tumor		
No	20	66.7
Yes (carcinoid syndrome or other)	10	33.3
Previous treatment		
Yes	16	53.3
No	14	46.7

Source: Table 1. Statistical Report v3.

* One patient had G3 NET, documented as protocol deviation during the study.

11.3 Measurements of treatment compliance

Not applied.

11.4 Efficacy results and tabulations of individual patient data

11.4.1 Analysis of Efficacy

Comparison of ^{68}GA-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT-CT

The first primary objective was to compare the sensitivity of ^{68}Ga-DOTATOC PET/CT to ^{99}mTc-Tektrotyd SPECT in NET patients. The performance of both imaging methods was analyzed and compared for the detection of primary tumor, loco-regional tumor (N1) and global tumor lesions (M1). A region was regarded positive if at least 1 lesion was detected in that region.

Additionally, number of detected lesions were also compared between both methods according to the location and involved organs as follows: 1) liver, 2) lung, 3) bone, 4) nodal infra, 5) nodal supra and 6) soft tissues of the body.

Differences in diagnostic performance (sensitivity) between the PET/CT and SPECT results were tested for significance using McNemar's test (two level of significance <0.05).

There was no statistically significant difference between the two imaging modalities in detection rate of primary tumor site (Table 3). Both modalities localized the site of the primary tumor in 11 of 28 patients (39%). All negative scans for primary tumor detection were considered false-negative.

In two patients, the primary lesion was found using ^{68}Ga-DOTATOC PET/CT imaging, but was not seen with ^{99}mTc-Tektrotyd SPECT. And in two other patients, the primary lesion was found using ^{99}mTc-Tektrotyd SPECT imaging, but was not seen with ^{68}Ga-DOTATOC PET/CT.

Table 3. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of primary tumor.

	^{99}mTc-Tektrotyd SPECT			**p-value**
^{68}Ga-DOTATOC PET/CT	Positive	Negative	Total	1.000
Positive	9 (81.8%)	2 (18.2%)	11 (39.3%)	
Negative	2 (11.8%)	15 (88.2%)	17 (60.7%)	
Total	11 (39.3%)	17 (60.7%)	28 (100%)	

Source: Table 132. Statistical Report v3. Data are presented as mean n (%).

^{68}Ga-DOTATOC PET/CT showed significantly hihger detection rate for loco-regional tumor versus ^{99}mTc-Tektrotyd SPECT (63.3% vs 43.3%; p = 0.034, Table 4). Thirty-seven percent of negative ^{99}mTc-Tektrotyd SPECT scans were positive on ^{68}Ga-DOTATOC PET/CT.

Table 4. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of loco-regional tumor (N1)

	^{99}mTc-Tektrotyd SPECT			*p*-value
68Ga-DOTATOC PET/CT	Positive	Negative	Total	0.034
Positive	12 (63.2)	7 (36.8)	19 (63.3)	
Negative	1 (9.1)	10 (90.9)	11 (36.7)	
Total	13 (43.3)	17 (56.7)	30 (100)	

Source: Table 133. Statistical Report v3. Data are presented as mean n (%).

There was no significant difference in detection of positive distant metastatic tumor lesions between ^{68}Ga-DOTATOC PET/CT and ^{99}mTc-Tektrotyd SPECT (100% vs 90%; p=0.083, Table 5).

Table 5. Comparison of ^{68}Ga-DOTA PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of global tumor lesions (M1)

	^{99}mTc-Tektrotyd SPECT			p-value
^{68}Ga-DOTATOC PET/CT	Positive	Negative	Total	0.083
Positive	27 (90)	3 (10)	30 (100)	
Negative	-	-	-	
Total	27 (90)	3 (10)	30 (100)	

Source: Table 134. Statistical Report v3. Data are presented as mean n (%).

Overall, significantly more metastatic lesions were detected with ^{68}Ga-DOTATOC PET/CT than with ^{99}mTc-Tektrotyd SPECT ($p < 0.002$). ^{68}Ga-DOTATOC PET/CT detected more than 20 lesions per patient in 53% of patients. On the contrary, ^{99}mTc-Tektrotyd SPECT detected less than 5 lesions per patient in the majority of cases (40%). (Table 6).

Table 6. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of global tumor (M1) – Number of lesions

		^{99}mTc-Tektrotyd SPECT				p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	10-20	>20	Total	0.002
<5	4 (80)	1 (20)	0	0	5 (16.7)	
5-10	3 (75)	1 (25)	0	3	14 (13.3)	
10-20	4 (80)	1 (20)	0	0	5 (16.7)	
>20	1 (6.3)	5 (31.3)	9 (56.3)	1 (6.3)	16 (53.3)	
Total	12 (40)	8 (26.7)	9 (30)	1 (3.3)	30 (100)	

Source: Table 135. Statistical Report v3. Data are presented as mean n (%).

Within the defined regions, significant more metastatic tumor lesions per patient were found with ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in liver (p=0.004, Table 7), infra-nodal (p= 0.05, Table 8) and supra-nodal regions (p=0.046, Table 9).

There were no statistically significant differences between either imaging procedures in detection of bone lesions, lung lesions and soft tissue lesions. (p >0.05) (Table 10, Table 11, Table 12).

Table 7. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of liver tumor lesions

		^{99}mTc-Tektrotyd SPECT			p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	10-20	Total	0.004
<5	8 (88.9)	1 (11.1)	0	9 (30)	
5-10	3 (100)	0	0	3 (10)	
10-20	2 (66.7)	1 (33.3)	0	3 (10)	
>20	1 (6.7)	8 (53.3)	6 (40)	15 (50)	
Total	14 (46.7)	10 (33.3)	6 (20)	30 (100)	

Source: Table 136. Statistical Report v3. Data are presented as mean n (%).

Table 8. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of infra-nodal lesions

	^{99}mTc-Tektrotyd SPECT		p-value
^{68}Ga-DOTATOC PET/CT	<5	Total	0.05
<5	24 (100)	24 (80)	
5-10	5 (100)	5 (16.7)	
10-20	1 (100)	1 (3.3)	
Total	30 (100)	30 (100)	

Source: Table 139. Statistical Report v3. Data are presented as mean n (%).

Table 9. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of supra-nodal lesions

	^{99}mTc-Tektrotyd SPECT		p-value
68Ga-DOTATOC PET/CT	<5	Total	0.046
<5	26 (100)	26 (86.7)	
5-10	4 (100)	4 (13.3)	
Total	30 (100)	30 (100)	

Source: Table 140. Statistical Report v3. Data are presented as mean n (%).

Table 10. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of lung lesions

	^{99}mTc-Tektrotyd SPECT		p-value
^{68}Ga-DOTATOC PET/CT	<5	Total	0.317
<5	29 (100)	29 (96.7)	
>20	1 (100)	1 (3.3)	
Total	30 (100)	30 (100)	

Source: Table 137. Statistical Report v3. Data are presented as mean n (%).

Table 11. Comparison of ^{68}Ga-DOTA PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of bone lesions

	^{99}mTc-Tektrotyd SPECT				p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	10-20	Total	0.261
<5	25 (100)	0 (0)	0 (0)	25 (83.3)	
5-10	2 (100)	0 (0)	0 (0)	2 (6.7)	
10-20	0 (100)	0 (0)	1 (100)	1 (3.3)	
>20	0 (0)	1 (50)	1 (50)	2 (6.7)	
Total	30 (100)	1 (33.3)	2 (6.7)	30 (100)	

Source: Table 138. Statistical Report v3. Data are presented as mean n (%).

Table 12. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{99}mTc-Tektrotyd SPECT in the detection of soft tissue lesions

	^{99}mTc-Tektrotyd SPECT		p-value
^{68}Ga-DOTATOC PET/CT	<5	Total	0.223
<5	27 (100)	27 (90)	
5-10	2 (100)	2 (6.7)	
>20	1 (100)	1 (3.3)	
Total	30 (100)	30 (100)	

Source: Table 141. Statistical Report v3. Data are presented as mean n (%).

Comparison of ^{68}GA-DOTATOC PET/CT vs ^{18}F-FDG PET/CT

The second primary objective was to compare the sensitivity of ^{68}Ga-DOTATOC PET/CT to ^{18}F-FDG PET/CT in NET patients. The performance of both imaging methods was analyzed and compared for the detection of primary tumor, loco-regional tumor (N1) and global tumor lesions (M1). A region was regarded positive if at least 1 lesion was detected in that region. Additionally, the number of lesions detected in six defined body regions were also compared between both methods.

Differences in diagnostic performance (sensitivity) between the PET/CT and SPECT results were tested for significance using McNemar's test (two level of significance <0.05).

No statistically significant difference in sensitivity was observed between the two imaging modalities in detection rate of primary tumor site (Table 16

In three patients, the primary lesion was found using ^{68}Ga-DOTATOC PET/CT imaging, but was not seen with ^{18}F-FDG PET/CT. And in one patient, the primary lesion was found using ^{18}F-FDG PET/CT imaging, but was not seen with ^{68}Ga-DOTATOC PET/CT.

Table 13). ^{68}Ga-DOTATOC PET/CT and ^{18}F-FDG PET/CT were true-positive for primary tumor in 11 patients (38%) and 9 patients (31%), respectively (p = 0.317). All negative scans for primary tumor detection were considered false-negative.

In three patients, the primary lesion was found using ^{68}Ga-DOTATOC PET/CT imaging, but was not seen with ^{18}F-FDG PET/CT. And in one patient, the primary lesion was found using ^{18}F-FDG PET/CT imaging, but was not seen with ^{68}Ga-DOTATOC PET/CT.

Table 13. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of primary tumor.

		^{18}F-FDG PET/CT		**p-value**
^{68}Ga-DOTATOC PET/CT	Positive	Negative	Total	0.317
Positive	8 (72.7)	3 (27.3)	11 (37.9)	
Negative	1 (5.6)	17 (94.4)	18 (62.1)	
Total	9 (31.0)	20 (69.0)	29 (100%)	

Source: Table 2. Statistical Report v3. Data are presented as mean n (%).

^{68}Ga-DOTATOC PET/CT showed significantly hihger detection rate for loco-regional tumor versus ^{18}F-FDG PET/CT (63.3% vs 20% positive patients; p <0.001, Table 14).

Sixty-eight percent of negative ^{18}F-FDG PET/CT scans were positive on ^{68}Ga-DOTATOC PET/CT. All negative ^{68}Ga-DOTATOC PET/CT scans in the detection of loco-regional lesions were also negative on ^{18}F-FDG PET.

Table 14. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of loco-regional tumor (N1)

		^{18}F-FDG PET/CT		**p-value**
^{68}Ga-DOTATOC PET/CT	Positive	Negative	Total	<0.001
Positive	6 (31.6)	13 (68.4)	19 (63.3)	

		^{18}F-FDG PET/CT		p-value
Negative	0	11 (100)	11 (36.7)	
Total	6 (20)	24 (80)	30 (100)	

Source: Table 3. Statistical Report v3. Data are presented as mean n (%).

^{68}Ga-DOTATOC PET/CT showed significantly hihger detection rate for global tumor lesions versus ^{18}F-FDG PET/CT (p= 0.002, Table 15). ^{68}Ga-DOTATOC PET/CT was positive for the detection of distant metastatic lesions (M1) in all patients vs 67% with the ^{18}F-FDG PET/CT.

Table 15. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of global tumor (M1)

		^{18}F-FDG PET/CT		p-value
^{68}Ga-DOTATOC PET/CT	Positive	Negative	Total	0.002
Positive	20 (66.7)	10 (33.3)	30 (100)	
Negative	-	-	-	
Total	20 (66.7)	10 (33.3)	30 (100)	

Source: Table 14. Statistical Report v3. Data are presented as mean n (%).

Overall, there were no significant differences between the two imaging modalities regarding the number of identified distant metastasis (M1) per patient. (Table 16).

Based on the location of lesions, there were no significant differences between either imaging procedure in the number of lesions identified in any of the regions (Table 17-Table 22).

Table 16. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of global tumor lesions (M1) – Number of lesions

			^{18}F-FDG PET/CT			p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	10-20	>20	Total	0.088
<5	3 (60)	1 (20)	0	1 (20)	5 (16.7)	
5-10	3 (75)	0	0	1 (25)	4 (13.3)	
10-20	4 (80)	1 (20)	0	0	5 (16.7)	

			^{18}F-FDG PET/CT			p-value
>20	3 (18.8)	1 (6.3)	4 (25)	8 (50)	16 (53.3)	
Total	13 (43.3)	3 (10)	4 (13.3)	10 (33.3)	30 (100)	

Source: Table 5. Statistical Report v3. Data are presented as mean n (%).

Table 17. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of liver lesions

		^{18}F-FDG PET/CT			p-value
^{68}Ga-DOTATOC PET/CT	<5	10-20	>20	Total	0.072
<5	8 (8.9)	0 (0)	1 (11.1)	9 (30)	
5-10	3 (100)	0 (0)	0 (0)	3 (10)	
10-20	2 (100)	0 (0)	1 (33.3)	3 (10)	
>20	4 (26.7)	4 (26.7)	7 (46.7)	15 (50)	
Total	17 (56.7)	4 (13.3)	9 (30)	30 (100)	

Source: Table 6. Statistical Report v3. Data are presented as mean n (%).

Table 18. Comparison of ^{68}Ga-DOTA PET/CT vs ^{18}F-FDG PET/CT in the detection of lung lesions

	^{18}F-FDG PET/CT		p-value
^{68}Ga-DOTATOC PET/CT	<5	Total	0.317
<5	29 (100)	29 (96.7)	
>20	1 (100)	1 (3.3)	
Total	30 (100)	30 (100)	

Source: Table 7. Statistical Report v3. Data are presented as mean n (%).

Table 19. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of bone lesions

	^{18}F-FDG PET/CT				p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	>20	Total	0.261
<5	25 (100)	0 (0)	0 (0)	25 (83.3)	
5-10	2 (100)	0 (0)	0 (0)	2 (6.7)	
10-20	0 (0)	1 (100)	0 (0)	1 (3.3)	
>20	1 (50)	0 (0)	1 (50)	2 (6.7)	
Total	28 (93.3)	1 (3.3)	1 (3.3)	30 (100)	

Source: Table 8. Statistical Report v3. Data are presented as mean n (%).

Table 20. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of infra-nodal lesions

	^{18}F-FDG PET/CT			p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	Total	0.160
<5	23 (95.8)	1 (4.2)	24 (80)	
5-10	5 (100%)	0 (0)	5 (16.7)	
>20	1 (100)	0 (0)	1 (3.3)	
Total	29 (96.7)	1 (3.3)	30 (100)	

Source: Table 9. Statistical Report v3. Data are presented as mean n (%).

Table 21. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of supra-nodal lesions

	^{18}F-FDG PET/CT			p-value
^{68}Ga-DOTATOC PET/CT	<5	5-10	Total	0.180
<5	25 (96.2)	1 (3.9)	26 (86.7)	
5-10	4 (100%)	0 (0)	4 (13.3)	
Total	29 (96.7)	1 (3.3)	30 (100)	

Source: Table 10. Statistical Report v3. Data are presented as mean n (%).

Table 22. Comparison of ^{68}Ga-DOTATOC PET/CT vs ^{18}F-FDG PET/CT in the detection of soft tissue lesions

	^{18}F-FDG PET/CT		p-value
^{68}Ga-DOTATOC PET/CT	<5	Total	0.223
<5	27 (100)	27 (90)	
5-10	2 (100%)	2 (6.7)	
>20	1 (100)	1 (3.3)	
Total	30 (100)	30 (100)	

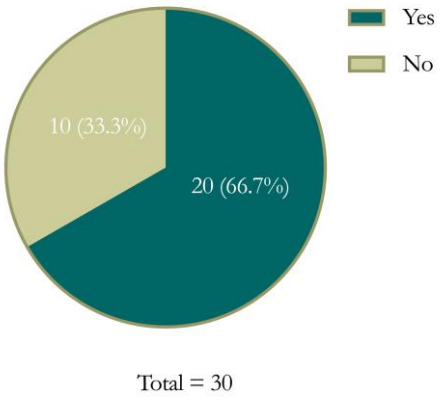
Source: Table 11. Statistical Report v3. Data are presented as mean n (%).

Change in therapeutic decision

The impact of additional data provided by ^{68}Ga-DOTATOC PET/CT on the patient's management was assessed.

As a result of the combined imaging modalities, therapeutic management changed in 20/30 patients (67%). (Figure 2).

Figure 2. Change in therapeutic decision



11.4.2 Statistical and analytical issues

Statistical and analytical issues are discussed in Section 9.7.

11.4.3 Tabulation of individual response data

By-patient listings of efficacy response data are included in Appendix **¡Error! No se encuentra el origen de la referencia.**.

11.4.4 Drug dose, drug concentration and relationships to response

Not applicable.

11.4.5 Drug-drug and drug-disease interactions

Not applicable.

11.4.6 By-patient displays

Individual patient data generated from clinical database for all patients are provided in Appendix **¡Error! No se encuentra el origen de la referencia.**.

11.4.7 Summary of efficacy results

The study included 30 patients. The median age for the whole study population was 58 years, with a range of 36-82 years, and 63% were male. Nearly half of patients had pancreatic cancer and 77% had G2/G3 differentiation.

The first objective was to evaluate the sensitivity of ^{68}Ga-DOTATOC PET/CT compared with ^{99}mTc-Tektrotyd SPECT in NET patients. There was no statistically significant difference between the two imaging modalities in detection rate of primary tumor site (39% in both modalities). However, ^{68}Ga-DOTA PET/CT showed significantly higher detection rate for loco-regional tumor versus 99mTc-Tektrotyd SPECT (63.3% vs 43.3%positive patients; p = 0.034). Moreover, significantly more metastatic lesions were detected with ^{68}Ga-DOTATOC PET/CT than with ^{99}mTc-Tektrotyd SPECT ($p < 0.002$). Specifically, significant more metastatic tumor lesions per patient were found in liver (p=0.004), infra-nodal (p= 0.05) and supra-nodal regions (p=0.046).

The second objective was to evaluate the sensitivity of ^{68}Ga-DOTATOC PET/CT compared with ^{18}F-FDG PET/CT in NET patients. There was no statistically significant difference between the two imaging modalities in detection rate of primary tumor site (38% with ^{68}Ga-DOTATOC PET/CT and 31% with ^{18}F-FDG PET/CT). However, ^{68}Ga-DOTA PET/CT showed significantly higher detection rate for loco-regional tumor and for global tumor lesions versus ^{18}F-FDG PET/CT ($p <0.001$). Based on the location of lesions, there were no significant differences between either imaging procedure in the number of lesions identified in any of the regions.

The change of management (third objective) took place in 67% of patients as a result of additional data provided by ^{68}Ga-DOTATOC PET/CT.

In conclusion, compared to routine ^{99}mTc-Tektrotyd SPECT and ^{18}F-FDG PET/CT imaging, ^{68}Ga-DOTATOC PET/CT appeared to have a greater sensitivity in the detection of loco-regional tumor. Moreover, ^{68}Ga-DOTATOC PET/CT compared to ^{99}mTc-Tektrotyd SPECT has de potential to detect more lesions in the liver, infra-nodal and supra-nodal regions.

12 Safety evaluation

12.1 Extent of exposure

An overall summary of the administered activity calculations (MBq) per radiopharmaceuticals are provided in Table 23 for all the patients exposed to study product.

Table 23. Administered activity calculations

	^{68}Ga-DOTATOC (n=30)	**^{18}F-FDG (n=30)**	**^{99}mTc-Tektrotyd (n=30)**
Dispensing syringe activity	180.4 (169.1; 192.4)	258.5 (225.7; 291.2)	593.9 (577.2; 625.3)
Minutes between administration and residual	1.0 (1.0; 2.0)	1.0 (1.0; 3.0)	5.0 (3.0; 5.0)
Dispensed dose	173.4 (161.5; 181.3)	249.6 (218.2; 282.8)	569.0 (548.3; 580.7)

Source: Table 3. Statistical Report v2. Data are presented as median (range).

12.2 Adverse events

12.2.1 Brief summary of adverse events

Two days after injection of the radiotracer ^{68}Ga-DOTATOC, a follow-up phone call was carried out to ask for and assess any experienced adverse events.

No immediate adverse reaction related to radiotracer injection was reported and the subjects reported no adverse events from the time of radioisotope injection until two days after the imaging probe.

12.2.2 Display of adverse events

No adverse events were observed in any of the patients.

12.2.3 Analysis of adverse events

No adverse events were observed in any of the patients.

12.2.4 Listing of adverse events by patient

No adverse events were observed in any of the patients.

12.3 Deaths, other serious adverse events and other significant adverse events

There were no deaths, serious adverse events and other significant adverse events reported in the study. Therefore, no listings were generated, and no narratives were required.

12.3.1 Deaths

There were no deaths during this study.

12.3.2 Other Serious Adverse Events

There were no serious adverse events reported in this study.

12.3.3 Other significant adverse events

No other significant adverse events were reported in this study.

12.3.4 Listing of deaths, other serious adverse events and other significant adverse events

No serious adverse events were noted.

12.3.5 Narratives of deaths, other serious adverse events and certain other significant adverse events

No serious adverse events were noted.

12.3.6 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

No other serious adverse events were noted.

12.4 Clinical laboratory evaluation

No laboratory evaluations were performed in this study.

12.5 Vital signs, physical findings and other observations related to safety

12.5.1 Vital signs

No alterations in vital signs, physical examination, or other observations were noted in any patient.

12.6 Summary of safety results

^{68}Ga-DOTATOC PET/CT imaging probe was well tolerated by all the participants, and no immediate or delayed adverse event was reported by the subjects during the two-day follow up after the radiotracer injection.

13 Discussion and overall conclusions

Our study demonstrates very good sensitivity of ^{68}Ga-DOTATOC PET/CT in the detection of metastatic NETs. Sensitivity of ^{68}Ga-DOTATOC PET/CT for detection of regional lymph node metastasis was 63.3% (vs. 43% with ^{99}mTc-Tektrotyd SPECT and vs. 20% with ^{18}F-FDG PET, both $p<0.05$). Additionally, ^{68}Ga-DOTATOC PET/CT showed a detection rate of 100% of distant metastasis compared to 67% with ^{18}F-FDG PET/CT ($p<0.05$). Although the positive rate for distant metastasis was similar to ^{99}mTc-Tektrotyd SPECT, ^{68}Ga-DOTATOC PET/CT showed a significantly higher number of identified distant lesions per patient.

^{68}Ga-DOTA PET/CT and ^{18}F-FDG PET/CT may be used for precise staging of patients with metastatic NETs, in which metastatic lesions may present heterogeneous metabolic activity and somatostatin receptor expression. However, in our study, detection rate of loco-regional and distant lesions did not increase when combining the two modalities. In fact, all negative ^{68}Ga-DOTATOC PET/CT scans in the detection of loco-regional lesions were also negative on ^{18}F-FDG PET. Moreover, ^{68}Ga-DOTATOC PET/CT showed a higher sensitivity than ^{18}F-FDG PET, probably because the patients included in our study had G1/G2 and well-differentiated NETs (Bahri et al. 2014). Neuroendocrine tumors with poor differentiation and a high grade have a decreased expression of somatostatin receptors, and, therefore, the ^{68}Ga-DOTATOC PET/CT scan may be negative, while FDG may be positive because of the increase in glycolytic metabolism (and the opposite is also true) (Liu et al. 2020). European Neuroendocrine Tumor Society guidelines recommend ^{18}F-FDG PET/CT in patients with NET of G3 grading (Deroose et al. 2016), and also in non-functioning tumors when patients have tumor-related symptoms. Large prospective studies are required to investigate the potential utility of combined modalities (^{68}Ga-DOTATOC PET/CT + ^{18}F-FDG PET/CT) in well-differentiated NET.

On the other hand, there were no statistically significant differences in detection rate of primary tumor site between the imaging modalities: 39.3% in both ^{68}Ga-DOTATOC PET/CT and 99mTc-Tektrotyd SPECT, and 31% in ^{18}F-FDG PET/CT. These results are similar or slightly lower to other reports (Prasad et al. 2010; Antunes et al. 2007; Schreiter et al. 2014; Alonso et al. 2014; Menda et al. 2017; Fallahi et al. 2019). In the previous study of Menda et al., ^{68}Ga-DOTATOC PET/CT identified the primary tumor in 38% of patients with metastases after conventional imaging failed to detect the primary lesion (Menda et al. 2017). Based on the location of metastatic lesions, ^{68}Ga-DOTATOC PET/CT detected significantly more lesions in liver, infra-nodal and supra-nodal regions compared with ^{99}mTc-Tektrotyd SPECT. Previous studies found that ^{68}Ga-DOTATATE PET/CT scanning is

superior to ^{111}In-pentetreotide SPECT/CT in the detection of primary and metastatic NET, although direct comparison with ^{68}Ga-DOTATOC PET/CT has not been performed (Sadowski et al. 2016).

One of the purposes of incorporating additional data provided by ^{68}Ga-DOTATOC PET/CT imaging is to help the clinicians in treatment planning. In our study, the management was change in 67% of patients after undergoing ^{68}Ga-DOTATOC PET/CT, a higher percentage than that observed in previous studies (Barrio et al. 2017), underlining the clinical impact of this imaging modality.

With regard to safety, there were no adverse events reported in the patients exposed to ^{68}Ga-DOTATOC. From available literature data, no adverse reaction related to ^{68}Ga-DOTATOC has been reported so far, when used in the specified diagnostic dose range. Therefore, no important risks have been noted. Gallium (^{68}Ga) edotreotide is generally well tolerated. There is, however, a hypothetical risk of hypersensitivity and adverse events related to exposure to ionizing radiation (induction of cancer and potential of hereditary defects).

The present study has some limitations. All of 30 patients had the three imaging tests done, but in an interval of 30 days, which could interfere with the comparison of the scans due to tumor proliferation during that period of time. Also, this was a unicentric study with a limited number of patients and no formal sample size calculation. Prospective studies with a larger patient group would be beneficial in the future.

In conclusion, our results showed very good sensitivity of ^{68}Ga-DOTATOC PET/CT in detection of the presence of loco-regional and distant metastases in patients with G1/G2 advanced NETs. Moreover, ^{68}Ga-DOTA PET/CT compared to ^{99}mTc-Tektrotyd SPECT has de potential to detect more lesions in the liver, infra-nodal and supra-nodal regions. ^{68}Ga-DOTA PET/CT, ^{18}F-FDG PET/CT and ^{99}mTc-Tektrotyd SPECT have a comparable diagnostic value in the detection of primary lesions of NETs. Therapeutic management of most patients changed after ^{68}Ga-DOTATOC PET/CT, underling the importance of ^{68}Ga-DOTATOC PET/CT incorporation into the clinical routine of NET patients.

14 Tables, figures and graphs referred to but not included in the text

NA.

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16 Signatures

I have read this Clinical Study Report and I confirm that it, to the best of my knowledge, accurately describes the conduct and results of the study.

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